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DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure; Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER 1952

ORIGINAL ARTICLES

THE HERITAGE OF HYPERTENSION* **

By Caroline Bedell Thomas, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

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The familial occurrence of hypertension is well recognized, but there is little agreement on the nature and number of the hereditary traits, or on the mode of genetic transmission. The trait most often regarded as a precursor of hypertension is circulatory lability appearing in youth and characterized by transitory elevations of blood pressure, arising spontaneously or in response to a standardized stimulus such as the cold pressor test[6,8,13,18]. Nevertheless, controversy surrounds the correlation of circulatory lability with familial hypertension, on the one hand, and with future hypertension for the hyperreactor on the other[1,2,5,7,9,10,21]. Equally divergent views exist in regard to the inheritance of hypertensive vascular disease itself. Studies based on family pedigrees showing multiple deaths from apoplexy in successive generations, or upon the family histories of patients hospitalized for hypertension, point towards its conveyance as a single Mendelian dominant trait[4,15]. When the family histories of life insurance applicants with and without high blood pressure are compared, however, little difference in incidence of familial hypertension is found between the 2 groups[3].

In view of these contradictions, stemming largely from differences in definition of hypertensive disease and in composition of the populations studied, we have approached the problem of the heredity of hypertension from a different point of view. Using the Johns Hopkins medical students as subjects, we have analyzed their family histories in regard to hypertension and related disorders, and have also determined the incidence of certain circulatory, metabolic and psychological characteristics in the subjects themselves[19]. Here I shall discuss the circulatory patterns of 84 subjects with history of hypertension in one or both parents, and compare them with the findings in our first 100 subjects whose parents are both free from hypertension. I shall also present some of the preliminary indications, derived from our genetic

* Read at the Sixty-fifth Annual Meeting of the Association of American Physicians, Atlantic City, New Jersey, May 6, 1952.

** This study was supported by Research Contract V1001M-2768, Veterans Administration.

data, that hypertension is inherited, and not as a single Mendelian dominant, but in a more complex fashion.

The diagnosis of hypertension is based on clinical information obtained by the medical student in consultation with his parents, often supplemented by actual blood pressure readings, and by reports from family physicians. Details are added after the student has enough clinical experience to appreciate the problems involved. Instances of essential hypertension predominate, but apparent cases of secondary hypertension are not excluded. A history of stroke is taken to indicate hypertension, although doubtless leading to an occasional error.

TABLE 1.—INCIDENCE OF HYPERTENSION AMONG 532 PARENTS OF MEDICAL STUDENTS

	Hypertension								
	Present		*Probable*		*Absent*		*Unknown*		
Parent	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Total*
Fathers	28	10.5	9	3.4	221	83.0	8	3.0	266
Mothers	33	12.4	16	6.0	210	78.9	7	2.6	266
Total	61	11.5	25	4.7	431	81.0	15	2.8	532

The incidence of hypertension among the parents of our subjects lies between 11 and 16%, as shown in Table 1, since in addition to those with definite hypertension, most of those in the "probable" group have intermittent or labile hypertension at present. The mothers, at a mean age of 55 years, have slightly more hypertension than the fathers at 57. Accordingly, since each subject has 2 parents, either of whom may be affected, almost 25% of medical students have a history of parental hypertension.

The determinants of circulatory lability to be considered are defined in Table 2. Five of these have been linked by others with an increased likelihood of future hypertension, namely, high resting blood pressure, transitory hypertension, transitory tachycardia, positive cold pressor test and overweight, whereas hyperreactivity to exercise was found by us to have a high correlation with parental cardiovascular disease[7,9,10,11,12,17,20]. Also, we have added a modification of "transitory tachycardia" called "high resting heart rate," since we rarely see our subjects under the "casual" conditions at which a heart rate of 100 or more is likely to be found. For brevity, these 7 determinants are hereafter referred to as "traits."

First, I show some individual patterns of circulatory lability as they appear in subjects with parental hypertension. General lability of blood pressure and heart rate is shown by the subject of Fig. 1, studied at intervals during 4 years in medical school. His mother had progressive hypertension first recognized at 39, leading to coronary occlusion, prolonged cardiac failure and death at 52. Most of the traits under consideration are present here. A blood pressure of 160/92 was recorded at the physical examination upon entering medical school. At rest in our laboratory, the diastolic level was always under 80, but the systolic level never came down below 120. The resting heart rate was quite variable. The cold pressor test showed a significant diastolic rise on 2 occasions, accompanied by acceleration of the heart.

TABLE 2.—DEFINITIONS OF 7 DETERMINANTS OF CIRCULATORY LABILITY.

High Resting Blood Pressure = 120 and/or 80 mm. or above.
High Resting Heart Rate = 80 or over.
Transitory Hypertension = Occasionally 150 and/or 90 mm. or above.
Transitory Tachycardia = Occasionally 100 beats per minute or above.
Positive Cold Pressor Test = Rise of 20 mm. systolic and/or diastolic.
Hyperreactivity to Exercise = Pulse pressure rise of 42 mm. and heart rate rise of 28 or more after exercise.
Overweight = 20 lbs. or more above "ideal" weight.*

* "Ideal" weight is based on tables published by the Association of life insurance directors and Actuarial Society of America, 1912.

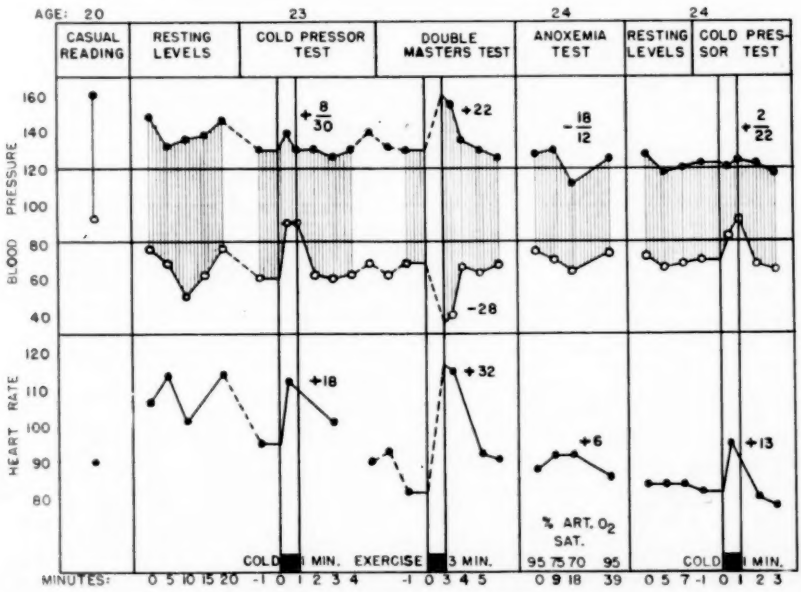

FIG. 1.—Subject 49M23. The Pattern of General Circulatory Lability.

Following 3 minutes of standard exercise over the Master steps, the pulse pressure widened and the heart speeded up to a degree shown by only 1/16 of our total unselected subjects. The anoxemia test, not otherwise included for discussion today, resulted in a fall in blood pressure as arterial oxygen saturation decreased, which is equally unusual[14].

Following the cold stimulus, a rise in blood pressure resulting mainly from vasoconstriction is generally considered the significant finding[8,16]. Subjects such as the one in Fig. 1, however, give evidence that the heart, as well, may actively participate in the circulatory response to cold. Cardiac lability is illustrated again in the duplicate positive cold pressor tests of another subject, whose father was found to have hypertension at 58 and died of a stroke at 61 (Fig. 2). Well marked cardiac acceleration was transiently present. On the second occasion, continuous ballistocardiographic tracings indicated that an increase of 37% in cardiac output occurred while the hand was immersed in ice water.

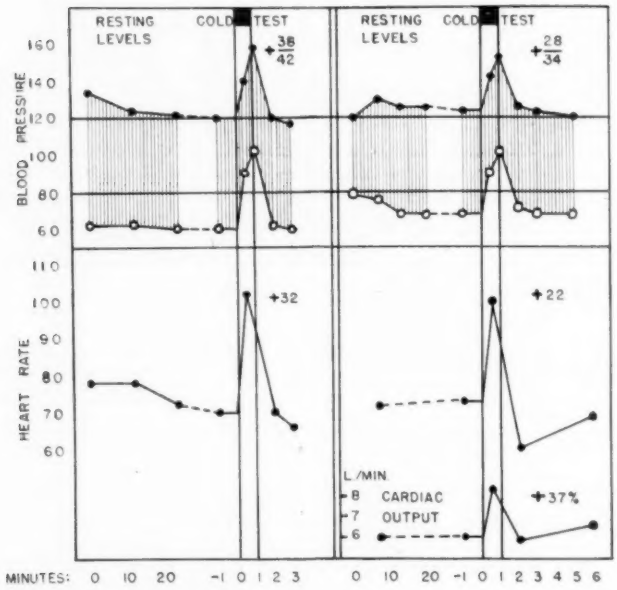

FIG. 2.—Subject 50M18. The Pattern of Hyperactivity to Cold with Cardiac Participation. Two positive cold pressor tests in the same subject. Cardiac output measured on a Starr-type ballistocardiograph.

The phenomenon of hyperreactivity to exercise also combines a change in blood pressure with acceleration in the heart rate. Exercise always produces a brief rise in systolic pressure; the diastolic pressure may rise, fall or remain unchanged[20]. Accordingly, the marked increase in pulse pressure found in hyperreactive individuals may be due to an excessive rise in systolic pressure, to an excessive fall in diastolic pressure, or to a moderate reciprocal change in both. The subject of Fig. 3, whose father at 54 has had asymptomatic hypertension for 2 years, showed hyperreactivity to exercise by an excessive rise in systolic pressure and heart rate on each of 2 tests. Cardiac output increased 64% immediately after exercise over the pre-exercise level. In contrast, an extreme example of the pattern of hyperreactivity to exercise with a fall in diastolic pressure is illustrated in the responses of 2 different subjects, each with a parent with asymptomatic hypertension (Fig. 4). For a brief period, the sounds over the brachial artery continued to be audible even when the blood pressure cuff was entirely deflated. The same phenomenon was observed in one of the subjects during recovery from the cold pressor test. So far we have had no opportunity to make ballistocardiographic studies on this rare form of circulatory lability. We do not know whether it is a coincidence that the only 2 subjects showing the pattern of hyperreactivity to exercise with "O" diastolic pressure, out of 433 who have had physiological studies, have had parents with elevated blood pressure[22]. We know, however, that around 75% of the subjects who show hyperreactivity to exercise in some form have a parental history of hypertension, often combined with coronary artery disease

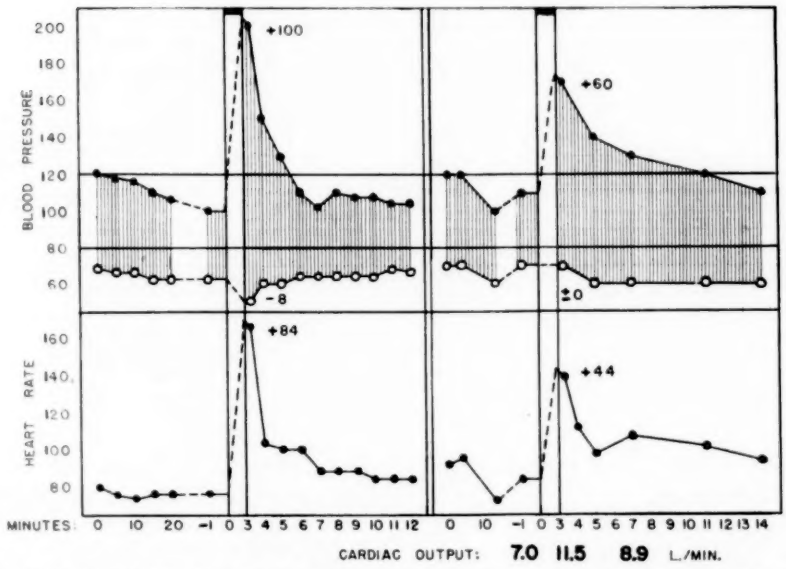

FIG. 3.—Subject 54M69. The Pattern of Hyperreactivity to Exercise. Two double Master exercise tests in the same subject.

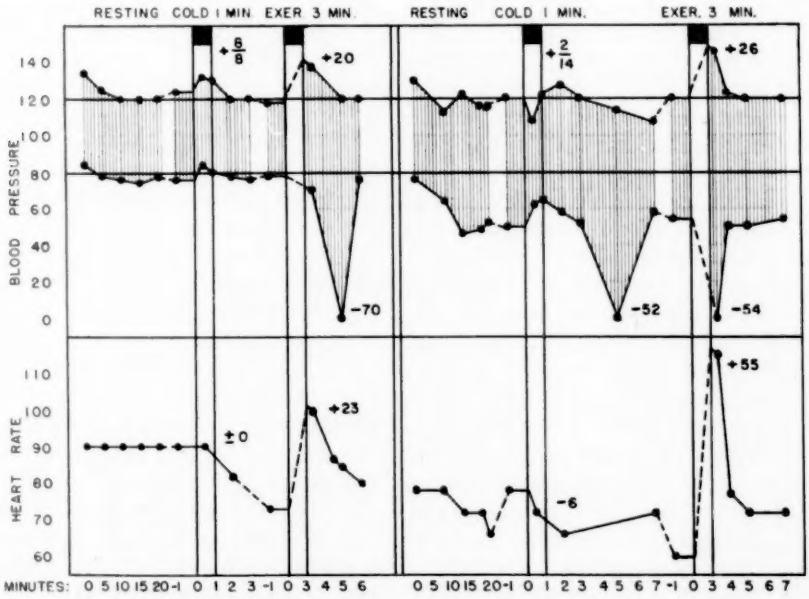

FIG. 4.—Subjects 49M14 and 49M10. The pattern of Transitory "O" Diastolic Pressure following Stress.

TABLE 3.—DETAILED PARENTAL HISTORY OF SUBJECTS SHOWING HYPERREACTIVITY TO EXERCISE

Father	*Mother*	*No. of subjects*
A. 11 Out of 84 Subjects with H + History		
H + and coronary occlusion	Negative	2
H +, asymptomatic	Negative	2
Died 34 nephritis	H +, stroke	1
Chronic nephritis	H +, asymptomatic	1
Died 49 H + and nephritis	Negative	1
Stroke, heart attack	Negative	1
Negative	H +, coronary occlusion, d. heart failure 52	1
Negative	H +, stroke, died coronary occlusion 58	1
Negative	H + asymptomatic	1
B. 3 Out of 100 Subjects with H— History		
Both parents negative		3

or nephritis in the same or the other parent (Table 3).

Not all subjects with parental hypertension show circulatory lability (Fig. 5). Among the subjects whose blood pressure and heart rate show little response to stress is a pair of identical twins, whose mother had hypertension at age 57 and a coronary occlusion followed by heart failure at 68. The resting blood pressures of the twins A and B are so much alike that if connecting lines were drawn between the 2 sets of observations they would appear to be consecutive readings on a single individual. Actually the twins were examined over 2 years apart for reasons relating to military service. In contrast to the similarity of their pressures, the heart rate of Twin B was consistently higher than that of Twin A. Both had negative cold pressor tests; no acceleration of the heart occurred in either twin. Diastolic pressure did not rise significantly on cold stimulation, or fall immediately after exercise. The rises in heart rate and systolic pressure after exercise in Twin A were about average for our subjects, while Twin B was hyporeactive to exercise.

What, then, is the incidence of the various traits related to circulatory lability among subjects with parental hypertension, and how does it compare with that found among subjects with normotensive parents? In Fig. 6 we see that the incidence of almost every one of the traits in question is definitely greater among the offspring of hypertensive parents. High resting blood pressure was the most frequent finding, occurring in 31% of the positive group, while high resting heart rate and a positive cold pressor test each occurred in 25%. However, of these 3 determinants, high resting heart rate shows the most striking contrast in incidence between the positive and negative groups, which again points toward the importance of the heart in circulatory lability, as does the differentiation associated with hyperreactivity to exercise.

If a close relationship exists between the inheritance of hypertension and circulatory lability, how is the presence of positive traits among the control group to be explained? First, there seems to be little significance attached to the finding of a single positive trait in an individual whose circulatory pattern is otherwise stable. When multiple traits pointing toward circulatory lability are present, however, the odds are more than 2 to 1 that such an indi-

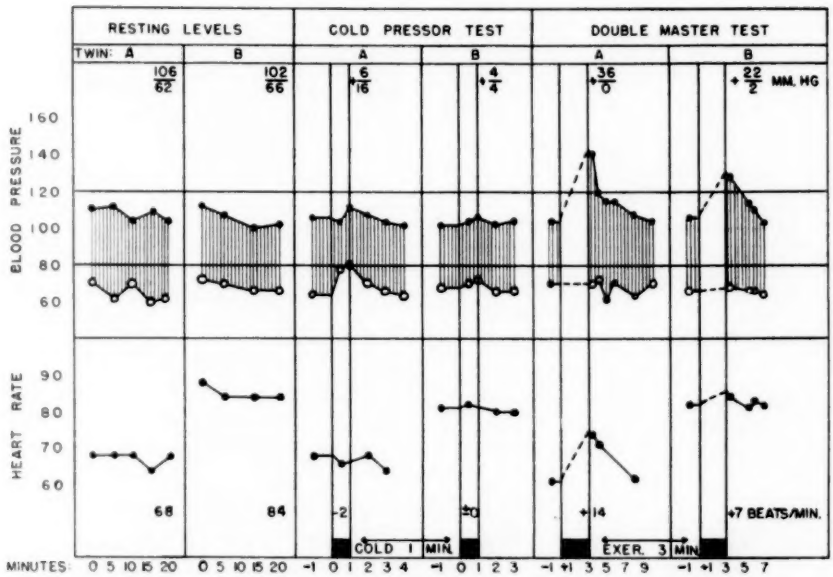

FIG. 5.—Subjects 48M20 (A) and 52M19 (B). The Pattern of Circulatory Stability in Identical Twins.

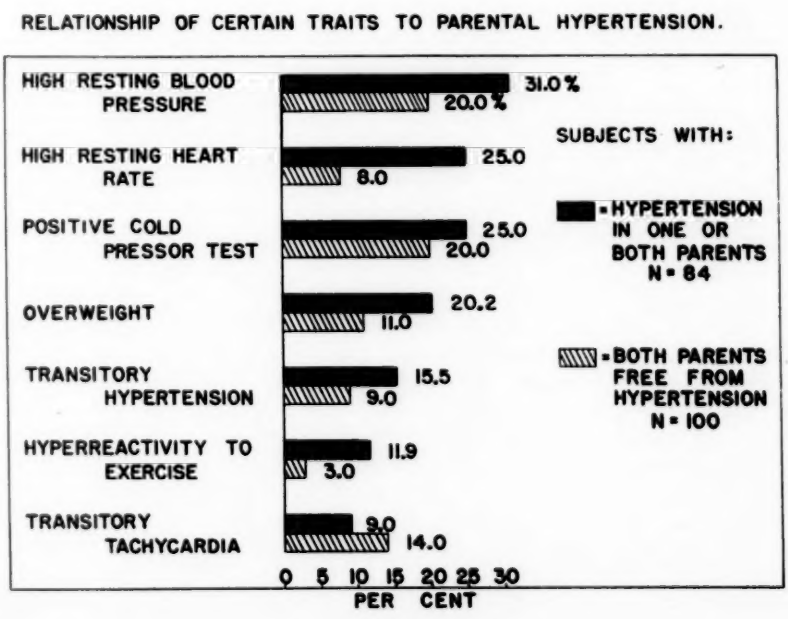

FIGURE 6

vidual has a parental history of hypertension. (Table 4). Thus 39.3% of the subjects with positive parental history show such evidence of circulatory lability, compared with 16.0% of the control group. As time goes on, some parents now non-hypertensive may be expected to develop hypertension. Every year several subjects with multiple positive traits do report such a change in parental history. More important, however, is the possibility that the inheritance of hypertension is recessive, so that hyperreactive individuals occasionally are born of parents with normal blood pressure who both carry the hypertensive trait.

The less conspicuous differences in incidence of hypertension between the 3 groups of male offspring is an interesting finding. Complementary evidence that the inheritance of hypertension is more manifest in the female line is shown in Fig. 8. Where mothers are hypertensive, twice as much hypertension is present in the maternal grandmothers as where mothers are normotensive. On the other hand, when fathers are hypertensive, twice as many paternal grandfathers have coronary artery disease as when fathers are normotensive. These differences, too, are statistically significant. Much

TABLE 4.—INCIDENCE OF MULTIPLE "POSITIVE TRAITS" ACCORDING TO THE PARENTAL HISTORY OF HYPERTENSION

Parental history	*No. of Subjects*	*Subjects with 2 to 6 "positive traits"*	
		No.	*%*
A. Hypertension Present (H+):			
1. Two parents with cardiovascular renal disease; one parent severely affected.	7	5	71.0
2. Two parents with uncomplicated H+.	8	3	37.5
3. One parent with complicated H+; one parent H−.	30	11	36.6
4. One parent with uncomplicated H+; one parent H−.	39	14	35.9
Total	84	33	39.3
B. Hypertension Absent (H−) in Both Parents.	100	16	16.0

We already have some genetic evidence that hypertension does not usually follow a simple dominant pattern* (Fig. 7). Going back to the grandparents' and parents' generations, the incidence of hypertension among the offspring of hypertensive persons is far lower than would be anticipated in a dominant type of inheritance. Hypertension is found among the female offspring of two hypertensive parents in 22.3%, compared with 4.4% of the female offspring of two non-hypertensive parents. This difference is statistically highly significant.

needs to be done, however, before the genetic interrelationship of hypertension and coronary artery disease is clearly understood.

Summary and Conclusion. We have found that circulatory lability is more prevalent among the offspring of hypertensive than of non-hypertensive parents. Where a significant correlation to parental hypertension exists, such lability is usually demonstrable in a number of different ways. The heart as well as the blood pressure frequently participates in the pattern of lability. The percentage of subjects showing

* Bernice H. Cohen has given valuable assistance and is collaborating in further analysis of the genetic data.

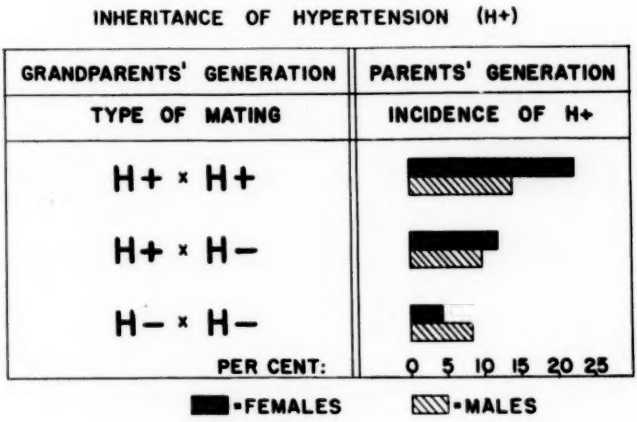

FIGURE 7

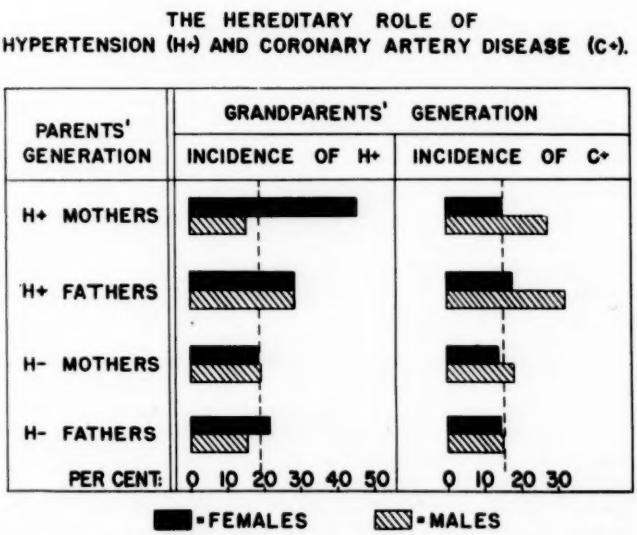

FIG. 8.— - - - line indicates the mean value for the incidence among grandparents where parents were H−.

circulatory lability is higher than the incidence of hypertension in the parents' generation, suggesting that additional factors are necessary for the appearance of hypertension. Preliminary genetic analysis indicates that hypertension bears an etiological relationship to coronary artery disease, and that the same heritage is expressed more often as hypertension in females and as coronary artery disease in males. While in some respects hypertension behaves like a single recessive gene widely distributed in the population, it seems probable that a more complex genetic pattern is involved.

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THE EFFECT OF THEOPHYLLINE WITH ETHYLENEDIAMINE (AMINOPHYLLINE) AND CAFFEINE ON CEREBRAL HEMODYNAMICS AND CEREBROSPINAL FLUID PRESSURE IN PATIENTS WITH HYPERTENSIVE HEADACHES*

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During an investigation of the cerebrovascular response to aminophylline administered intravenously, patients with hypertensive headaches reported that this drug frequently relieved their pain. It seemed possible that this was the result of altered intracranial hemodynamics because xanthines decrease cerebral blood flow[15] and reduce cerebrospinal fluid pressure in normal individuals[2,7]. To further elucidate this problem, the effect of aminophylline and caffeine on cerebral blood flow and oxygen metabolism in patients suffering from hypertensive headaches was studied. In addition, an attempt was made to evaluate any relationship between these changes and changes in cerebrospinal fluid pressure.

Materials and Methods. Thirteen patients who had hypertensive headaches were selected from the medical wards and the hypertensive clinic. Care was taken to select patients in whom the headaches definitely seemed to be secondary to the hypertension rather than due to some unrelated cause. A summary of the pertinent clinical data is found in Table 1. All patients had headaches which awakened them in the morning. The headaches were graded from 1 to 4, depending on the severity and duration of the present episode of pain at the time the study was performed. Grade 4 headaches were continuous for several days and required opiates for relief. The pain was most often occipital, but was frequently frontal or parietal and was often worse on one side. In only 1 patient (M.Y.) had the symptom of recurrent headaches antedated the known duration of the hypertension. In most cases, the headache was the major symptom of the disease and the reason for seeking medical care on the present admission. Three patients had chronic glomerular nephritis. Two of these had elevations of the BUN to 34 mg. per 100 cc. and 53 mg. per 100 cc. (J.B., J.D.),

* This investigation was supported (in part) by a research grant from the National Heart Institute, of the National Institutes of Health, Public Health Service.

TABLE 1.—SUMMARY OF CLINICAL STATUS OF PATIENTS WITH HYPERTENSIVE HEADACHES BEFORE AND AFTER AMINOPHYLLINE OR CAFFEINE

Case	Sex	Age	Diagnosis	Known Hypertension	Duration Headaches	Eye Grds.	V.P. C	V.P. A	Het.	R.R. C	R.R. A	P.R. C	P.R. A	B.P. C	B.P. A	Headache C	Headache A
Aminophylline																	
J. B.[1]	M	50	CGN	14 mos.	Int. 3 mos. Cont. 2 wks.	IV	100	90	38	24	24	90	94	244/138	224/124	++++	+
M. Y.	M	44	HCVD	4 mos.	Int. 1 yr.	II	40	—	38	25	22	92	102	200/130	230/130	++	++
A. L.	F	59	HCVD, CF (2+)[2]	2 yrs.	Int. 1 yr.	II	140	80	36	31	19	74	78	170/115	179/113	++	0
J. D.[3]	M	56	CGN	4 mos.	Int. 3 mos. Cont. 2 days	IV	90	—	36	34	37	110	113	182/142	168/117	++++	+
B. J.[3]	F	46	HCVD, CF (2+)[2]	4 yrs.	Int. 2 yrs.	I	135	110	48	20	30	86	90	220/115	170/105	++	0
F. D.[3]	F	48	HCVD, CF (2+)[2]	15 yrs.	Int. 6 yrs.	II	210	200	36	15	22	80	64	184/110	150/110	+++	++
E. R.	F	50	HCVD	3 yrs.	Int. 1 yr.	II	118	105	41	21	20	88	100	170/115	165/110	+++	+
E. K.	F	56	HCVD, CF (3+)[2]	9 yrs.	Int. 6 mos.	III	175	130	42	40	34	136	120	240/140	212/130	++	0
C. J.	M	57	HCVD, SHD	?	Int. 2 mos.	III	110	90	42	42	37	100	96	270/90	240/98	+	0
Mean		52					141[5]	115[5]	40	28	27	95	95	209/122	193/115		
Caffeine																	
M. G.	F	51	HCVD	5 yrs.	Int. 1 yr.	III	73	76	32	18	20	100	96	204/104	204/110	+	0
E. K.[4]	F	57	HCVD, CF, comp.	9 yrs.	Int. 6 mos.	III	96	115	56	18	24	78	72	160/110	160/110	+	+
R. T.	F	45	HCVD, CF (1+)[2]	6 yrs.	Cont. 1 mo.	III	86	86	46	20	18	72	64	255/135	274/134	++	+
E. W.	M	46	CGN	3 mos.	Int. 1 mo.	IV	110	92	35	20	22	80	82	230/120	240/120	+	0
J. H.	M	34	HCVD	1 yr.	Int. 6 mos.	IV	100	80	38	26	30	90	90	214/142	230/150	+++	+
B. J.	F	46	HCVD	4 yrs.	Int. 2 yrs.	I	130	120	38	20	20	72	80	180/110	200/120	++	0
J. B.[3]	M	50	CGN	14 mos.	Int. 3 mos.	IV	85	90	36	20	20	94	94	184/100	194/104	++	0
Mean		47					97	94	40	20	22	84	83	204/117	215/121		

Eye Grds.—Retinopathy graded in severity from I to IV
V.P.—Venous pressure, mm. water measured at jugular bulb, except E.R. and B.J. in whom it was measured in the antecubital vein.
Het.—Hematocrit
R.R.—Respiratory rate
P.R.—Pulse rate
B.P.—Blood pressure, ausculatory
CGN—Chronic glomerular nephritis
HCVD—Hypertensive cardiovascular disease
CF—Cardiac failure
SHD—Syphilitic heart disease
comp.—compensated
Int.—Intermittent
Cont.—Continuous

C—Control
A—After aminophylline or caffeine

[1] Azotemia—J.B. = 34 mg./100 cc. J.D. = 53 mg./100 cc.
[2] Clinical manifestations, criteria Am. Ht. Assn.
[3] Patient developed hyperventilation, sweating, and carpal spasm after aminophylline.
[4] Patient developed signs of nervous irritability, tremor, pallor, & sweating after aminophylline.
[5] Mean for only those patients on which the determination was done before and after aminophylline.
[6] Cheyne-Stokes respiration which was arrested after caffeine administration.

Circulation time—Decholin .5 cc. I.V.

TABLE 2.—EFFECT OF AMINOPHYLLINE AND CAFFEINE ON CEREBRAL HEMODYNAMICS IN PATIENTS WITH HYPERTENSIVE HEADACHES

	Art. CO_2 Vol.%		*Ven. CO_2 Vol.%*		*Art. pCO_2*		*Ven. pCO_2*		*Art. O_2 Vol.%*		*Ven. O_2 Vol.%*		*A-V O_2 Vol.%*		*CBF*		*$CMRO_2$*		*MBP*		*CVR*		*CSFP*	
	C	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*	*C*	*A*
Aminophylline																								
J. B.[3,5]	29.0	29.8	34.8	37.8	25	26	30	32	15.1	14.5	8.5	5.7	6.6	8.8	63	38	4.2	3.3	173	157	2.7	4.1	280	174
M. Y.	31.1	30.8	39.5	39.2	—	—	—	—	14.6	14.7	5.8	6.0	8.8	8.7	47	50	4.1	4.4	153	163	3.3	3.3	156	160
A. L.[2]	29.5	24.6	35.0	33.5	—	—	—	—	17.6	17.8	10.8	9.7	6.8	8.1	44	30	3.0	2.4	133	135	3.0	4.5	—	—
J. D.[3]	19.2	18.8	25.8	26.0	—	—	—	—	11.9	12.8	5.4	4.1	6.5	8.7	55	25	3.6	2.2	155	134	2.8	5.4	—	—
B. J.[5,6]	39.4	33.4	45.3	41.0	44	37	46	42	16.0	17.6	10.8	9.2	5.2	8.4	74	38	3.8	3.2	150	127	2.0	3.3	270	110
F. D.[3]	37.6	36.6	45.2	46.2	32	29	39	42	16.2	18.1	7.2	8.4	9.0	9.7	43	49	3.9	4.8	135	123	3.1	2.5	—	—
E. R.	38.4	37.0	48.4	47.0	—	—	—	—	16.0	18.2	11.2	7.2	4.8	11.0	59	36	2.8	4.0	133	128	2.3	3.6	170	110
E. K.[2,5]	24.9	22.8	33.7	31.1	28	26	38	35	16.6	15.9	9.4	8.4	7.2	7.5	58	35	4.2	2.6	173	157	3.0	4.5	172	108
C. J.	38.4	36.8	45.9	48.6	—	—	—	—	15.6	16.2	7.4	4.3	8.2	11.9	32	20	2.6	2.4	150	145	4.7	7.3	—	—
Mean	31.9	30.1	39.3	38.9	32	29	38	38	15.5	16.2	8.5	7.0	7.0	9.2[7]	53	36[7]	3.6	3.3	151	141	3.0	4.3[8]	210	132[9]
Caffeine																								
M. G.	43.4	45.0	51.0	52.8	33	35	37	39	14.4	15.8	8.2	9.4	6.2	6.4	62	54	3.8	3.5	137	141	2.2	2.6	115	115
E. K.[5]	51.0	52.3	61.0	60.6	36	35	51	46	18.1	19.9	9.3	9.7	8.8	10.2	40	34	3.5	3.5	127	127	3.2	3.7	180	120
R. T.[2]	24.1	23.8	29.1	29.0	34	33	42	41	15.6	16.1	9.4	8.4	6.2	7.7	53	60	3.3	4.6	175	181	3.3	3.0	142	150
E. W.[5]	51.6	52.6	55.0	57.8	38	40	45	46	8.8	10.7	5.0	4.5	3.8	6.2	50	39	1.9	2.4	157	160	3.1	4.1	—	—
J. H.	45.1	45.6	50.6	51.1	34	29	44	39	12.7	12.7	8.1	6.0	4.6	6.7	55	48	2.5	3.2	166	177	3.0	3.7	210	210
B. J.[5]	37.2	39.8	43.5	48.4	36	36	39	42	13.9	13.6	9.9	7.9	4.0	5.7	70	50	2.8	2.9	133	147	1.9	2.9	215	110
J. B.[3,5]	31.4	31.2	36.4	39.6	—	—	—	—	16.8	17.0	8.3	8.1	8.5	8.9	51	46	4.3	4.1	128	134	2.5	2.9	—	—
Mean	40.5	41.5	46.7	48.5	35	35	43	42	14.3	15.1	8.3	7.7	6.0	7.4	54	47	3.2	3.5	146	152	2.7	3.3[10]	172	141

[1] Azotemia—J.B. = 34 mg. 100cc . J.D. = 53 mg. 100 cc.
[2] Patients receiving ammonium chloride as a diuretic within 2 weeks before the cerebral blood flow studies were done.
[3] Patient developed tremor, sweating, irritability and cold clammy skin.
[4] Associated pulmonary disease with depressed pulmonary ventilation.
[5] Patients receiving both caffeine and aminophylline on different days.
[6] Hyperventilation after aminophylline.
[7] Statistically significant change from control value ($p < 0.01$).
[8] Statistically significant change from control value ($p = 0.03$).
[9] Statistically significant change from control value ($p = 0.08$).
[10] Statistically significant change from control value ($p = 0.05$).

pCO_2 —Partial pressure of CO_2
Ven. O_2—Jugular bulb
CBF —Cerebral blood flow, cc./100 gm. brain/min.
$CMRO_2$—Oxygen consumption, cc./100 gm. brain/min.
CVR —Cerebrovascular resistance = $\frac{MBP.}{CBF}$
MBP —Mean arterial blood pressure. diastolic + pulse pressure/3
CSFP —Cerebrospinal fluid pressure, mm. water.
C —Control
A —After aminophylline or caffeine, 0.5 gm. I.V. (5 min. for administration)

but no symptoms of uremia. One patient (C.J.) had aortic insufficiency due to syphilis. Five patients exhibited cardiac failure with peripheral edema and signs of pulmonary congestion. The circulation times (arm to tongue) in these patients varied from 20 to 50 seconds. The hemoglobin was not below 11 gm. in any of the patients.

The effect of aminophylline was studied on 9 patients (Group 1) and the effect of caffeine on 7 (Group 2). The response to both drugs was determined in 3 of the patients for purposes of comparison. However, each drug was administered on a different day. The subjects were studied in a fasting state and in the supine position. Measurements of the pulse rate, respiratory rate, and blood pressure (auscultatory) were taken during the control period and repeatedly during the course of each experiment. A control cerebral blood flow study was performed employing the nitrous oxide method[6]. Fifteen minutes later 0.5 gm. of aminophylline or caffeine-sodium-benzoate in 50 cc. of normal saline was given intravenously over a 10-minute period. A second cerebral blood flow determination was performed 5 minutes later. After the blood samples were drawn, pH determinations were done on a Beckman pH meter using a drop electrode. The Van Slyke nomogram[12] was used to estimate pCO_2. Cerebral oxygen consumption ($CMRO_2$) and cerebrovascular resistance (CVR) were calculated as previously described[6]. The Van Slyke-Neill manometric apparatus was used for the gas analysis and aerosol was used as the hemolytic agent[17].

The effect of aminophylline and caffeine on the cerebrospinal fluid pressure was measured at a later date, employing the same method of drug administration. Pressures were measured in the recumbent position and precautions were taken to avoid jugular compression, straining, and loss of cerebrospinal fluid. The pressures were allowed to stabilize before taking the readings and were recorded before the administration of the drug and at 5-minute intervals for 30 minutes thereafter.

Results. The effect that aminophylline and caffeine had on the headaches is recorded in Table 1. There was immediate relief of headaches following the administration of aminophylline in 7 instances. There was equivocal relief in 1 (F.D.) and no relief in the ninth (M.Y.). After caffeine, relief of headache was obtained in 5 out of 7 patients. In 1 patient the response was equivocal (R.T.), and in another (E.K.) no relief was obtained. The relief of headache was more rapid and lasted longer after aminophylline (several hours to as long as 1 week). It is noteworthy that headaches associated with papilledema occurring in patients with renal failure and malignant hypertension, obtained relief which was frequently more complete than after using opiates. A summary of the data on the spinal fluid pressure and cerebral hemodynamics is found in Table 2.

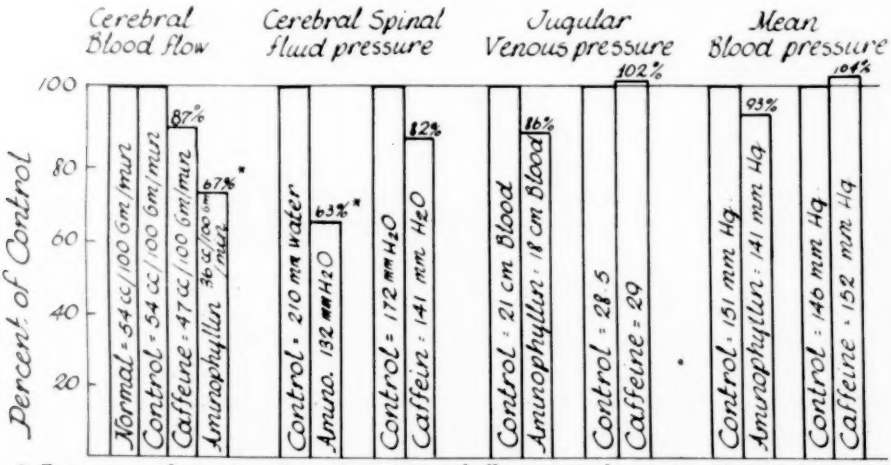
Following the administration of aminophylline, the cerebrovascular resistance, which was already above normal, rose from 3.0 to 4.3 ($p=0.03$). The cerebral blood flow, which was normal during the control study, fell from an average rate of 53 cc./100 gm. brain/min. to 36 cc./100 gm. brain/min. ($p<0.01$). Only 2 of the patients did not show a reduction in cerebral blood flow, both of whom did not obtain relief of their headaches. One of these developed side reactions consisting of nervousness, sweating, and tremor[15]. For the group as a whole, there was not a statistically significant change in either arterial or venous pCO_2 or CO_2 content. There was a significant increase in the A-V O_2 difference from 7.0 to 9.2 volumes per cent ($p<0.01$) due to both an increase of arterial oxygen and a decrease in venous oxygen content. The oyxgen consumption ($CMRO_2$) was not altered significantly (3.6 to 3.3 cc/100 gm. brain/min.). The blood pH was not affected appreciably by aminophylline. For example, the mean arterial blood pH was 7.46 before aminophylline and 7.48 after it. The venous blood pH was 7.42 before as well as after the drug.

The cerebral hemodynamic changes after caffeine were similar to those

after aminophylline, but were less pronounced and consequently not as highly significant statistically. There were no significant changes in arterial or in venous CO_2. The cerebral blood flow fell from 54 to 47 cc./100 gm./min. ($p = 0.12$). The cerebrovascular resistance increased from 2.7 to 3.3 ($p = 0.05$). There was an increase in A-V O_2 from 6.0 to 7.4, which statistically was not significant. The $CMRO_2$ did not change (3.2 to 3.5 cc./100 gm./min.).

In Group 1 the average cerebrospinal fluid pressure fell from 210 mm. to 132 mm. water ($p = 0.08$) following the administration of aminophylline. The 141 mm. The jugular venous pressure, pulse rate, arterial blood pressure, and respiratory rate were unchanged. The percentile relationship between the more important dynamic changes can easily be compared in Fig. 1.

Discussion. Although the lowering of cerebrospinal fluid pressure after aminophylline administration was frequently associated with some reduction in jugular venous pressure, the two were not closely related (Tables 1 and 2). The cerebrospinal fluid pressure decreased considerably more than the jugular pressure. Futhermore, caffeine, which has essentially the same cerebrovascular action as aminophyl-



Caffeine mean observation, 7 patients; Aminophylline mean observation, 9 patients.
* Statistically significant.

FIG. 1—Cerebral hemodynamics and cerebrospinal fluid pressure changes after caffeine and aminophylline are compared with the control values for these same patients.

decrease in spinal fluid pressure was quite marked in all but 1 patient thus studied. The average jugular venous pressure declined from 141 to 115 mm. of water. The mean blood pressure, pulse rate, and respiratory rate did not change significantly. After caffeine administration (Group 2), the cerebrospinal fluid pressure fell from 172 to

line, frequently caused a decrease in cerebrospinal fluid pressure[7], yet it did not appear to effect jugular venous pressure. The authors feel that the sharp decrease in cerebral blood flow is the most likely reason for the reduction in spinal fluid pressure observed after the administration of aminophylline and caffeine. This relationship is seen in

Fig. 2. The increased resistance at the arteriolar level results in a decrease in cerebral blood inflow and tends to decrease the volume of blood in the brain and consequently the pressure within the post arteriolar (capillary and venous) system. This quickly decreases cerebrospinal fluid pressure, since the intracranial contents are quite flexible and the pressures easily transmitted between the intracranial blood reservoirs and the cerebrospinal fluid. Goldensohn *et al.*[3] have shown the opposite effect can also be demonstrated, for when the arterioles are dilated and the cerebral blood flow increased by administering CO_2, the cerebrospinal fluid pressure rises sharply, apparently due to an increase in blood volume within the cranium. Under the latter circumstances, one can actually observe arterial pulsations which are transmitted to the cerebrospinal fluid.

Although the ability of the xanthines to reduce the spinal fluid pressure is an interesting pharmacodynamic observation, can it be said that there is any relationship of this phenomenon to the relief of headaches obtained after aminophylline and caffeine? Certainly, during the control studies, there was no correlation observed between the severity of the headaches and the cerebrospinal fluid pressure. In fact, only 4 out of 10 patients exhibited cerebrospinal fluid pressure above 200 mm. water. Furthermore, Shelburne *et al.*[13] have shown that decreasing the cerebrospinal fluid pressure by removing fluid does not improve the headaches. Therefore, we must conclude that the relief of "hypertensive headaches" noted in the present study is not the result of the decrease in cerebrospinal fluid pressure alone. As noted below, it is more likely the direct effect of aminophylline and caffeine on the cerebral vasculature[9,15] and the relief of vascular distention which is responsible for this beneficial result.

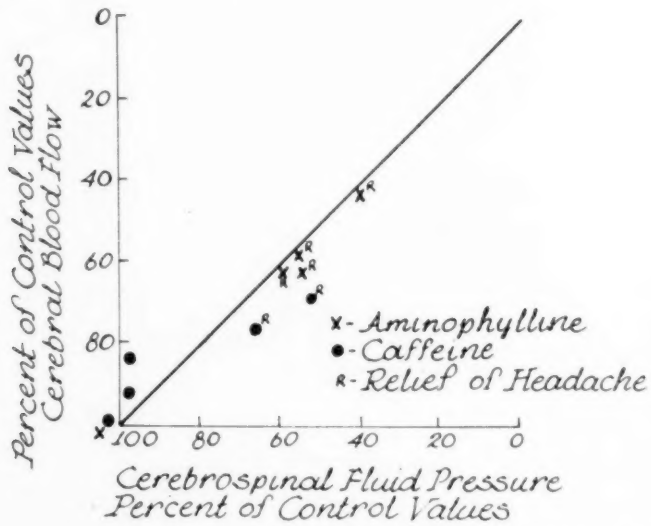
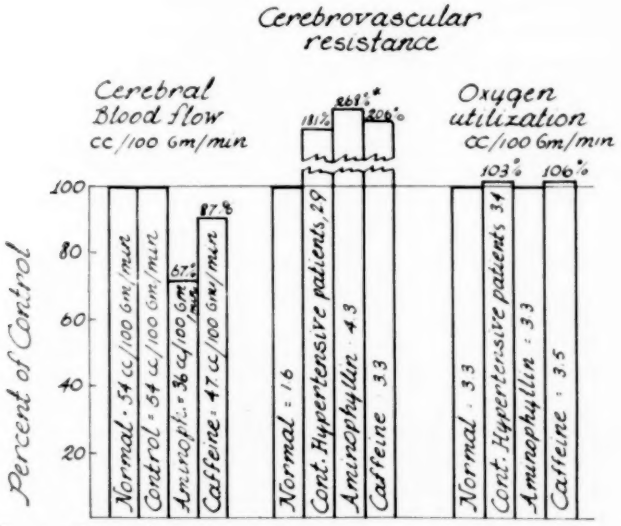


FIG. 2—The percentage decrease of cerebral blood flow after caffeine (•) and aminophylline (x) is plotted against the decrease in cerebrospinal fluid pressure. There appears to be a good correlation.

Although the mechanism of "hypertensive headaches" has never been proven conclusively, it has been generally accepted that they cannot be closely correlated with the level of blood pressure alone[16]. Wolf[16] describes 2 types of headache which are secondary to hypertension: (1) encephalopathic headaches, and (2) headaches due to imbalance between vascular tone of the cranial arteries and the blood pressure. In the former, headaches result from high intracapillary and filtration pressure in the brain, which produce cerebral edema and traction on pain sensitive structures. In the latter, the cranial, rather than the cerebral vessels, are supposedly involved. As the pressure rises, the arterial tone is not increased proportionally, thus producing an increased pulsation and stretching of the cranial arteries with simulation of pain receptors. This is essentially the same mechanism of origin that Wolf has described in migraine[16] headaches due to involvement of the cranial arteries. In the hypertensive headache, it is the increased intravascular pressure which is primarily responsible for the arterial distention, but in the true migraine, excessive relaxation of the artery (decreased vascular tone) is primarily responsible. Although distention of the cranial arteries may be primarily responsible for the production of many hypertensive headaches (nonencephalopathic), it is difficult to correlate this concept with the relief of the headaches noted in the present study because intravenous caffeine[16] actually increases pulsations of the cranial vessels. It seems quite likely that distention of the cerebral arteries is the more important factor. Anatomically this is quite possible since Moench[8] has shown that pain arising from the cerebral arteries is referred to the cranium. The increase in cerebrovascular resistance and decrease in cere-



* Statistically significant change.

FIG. 3—Effects of aminophylline and caffeine on cerebral hemodynamics and oxygen metabolism in patients with hypertension. These results are compared graphically with normal values.

bral blood flow after aminophylline and caffeine indicates that these drugs cause cerebral arterial constriction. This was accompanied by relief of the headaches. We might thus conclude that increased tone and decreased distention of the cerebral arteries rather than of the cranial arteries, is the mechanism whereby the relief of the headaches was obtained. Veriloid administered intravenously produces the same symptomatic relief[10] by lowering the blood pressure and thus relieving the cerebrovascular distention. This also explains why "hypertensive headaches" are aggravated in the supine position wherein the "effective" cerebral arterial pressure is increased[11]. If these conclusions are correct, it is probably true that "hypertensive headaches" arise from distention of the cerebral, rather than the cranial arteries, in many instances. In this type of headache, there would be no overall correlation between the degree of hypertension and the incidence of headaches in any group of patients. For the individual patient, however, there would be a definite relationship between the severity of the headache and the height of the blood pressure, if the vascular tone was not altered. The greater the disparity between vascular tone and the blood pressure, the greater the vascular distention would be and the more severe and more frequent would be the headaches.

The encephalopathic headache (of which there were 4 in the present study) may have essentially the same origin as the milder nonencephalopathic "hypertensive headache," the former merely representing an advanced phase of the latter. In the early phases of encephalopathy, the increased blood pressure associated with high cerebrovascular resistance may cause an increased lateral pressure on the cerebral arteries resulting in vascular distention and pain[8]. If the hypertension becomes severe and progressive, pressure is, in addition, transmitted to the post-arteriolar capillary system, which causes an increase of pressure in this segment. This leads to encephalopathy because of increased diffusion of plasma into the tissue, resulting in edema and increased tissue pressure[4]. Thus, more pain is produced by traction and pressure upon pain sensitive intracranial structures (meninges, tentorium, or large venous sinuses). Cerebral blood flow and cerebral metabolism as reflected in oxygen uptake are normal; and therefore, are inconsequential in production of the syndrome. Aminophylline and caffeine temporarily relieve the symptoms not by reversing the process but by increasing the cerebrovascular tone and cerebrovascular resistance, thus decreasing the arterial vascular distention. In addition to the effect on arterial distention, in the encephalopathic state (cerebral edema) the increased cerebrovascular resistance produced by aminophylline results in less pressure being transmitted to the postarteriolar capillaries. Thus, there is a decrease in capillary blood pressure and consequently a decrease in diffusion pressure. This results in emigration of fluid from the tissue back into the capillaries. Pressure or traction on pain sensitive intracranial structures is relieved, resulting in more relief of the headache. Caffeine and aminophylline had opposite effects on the systemic blood pressure and jugular venous pressure, so that it seems unlikely that either of these factors influenced the relief of the headaches.

In evaluating this therapeutic response to aminophylline and caffeine, it is essential that the headaches resulting from the high blood pressure be differentiated from the numerous nondescript types of headache that oc-

cur in patients with hypertension. The latter types, which occur more frequently[16], usually antedate the hypertension, and, in the authors' experience, are not effectively or consistently relieved with the xanthines. The observations in the present study have been limited to true "hypertensive headaches" which, as determined from the history, seemed to result definitely from the "high blood pressure."

Summary. 1. Aminophylline and caffeine cause prompt relief of headaches which result from the hypertensive state. Aminophylline is the more effective agent in this respect. The presence of kidney disease or heart failure does not alter this response. The data suggest that caffeine and aminophylline decrease the arterial and postarteriolar vascular distention of the cerebral vessels and thus relieve the headache. If relief is to be anticipated, it is necessary to determine that the headache is due to the hypertension and not to some unrelated cause.

2. Both aminophylline and caffeine cause an increase in cerebrovascular resistance with a decrease in cerebral blood flow. This is followed by a fall in spinal fluid pressure. Therefore, aminophylline is an effective agent for acutely reducing cerebrospinal fluid pressure in patients with hypertension. The fall in cerebrospinal fluid pressure is secondary to a decrease in cerebral blood flow.

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STIGMONENE BROMIDE IN THE DIAGNOSIS OF EARLY PREGNANCY AND THE TREATMENT OF SIMPLE DELAYED MENSTRUATION

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For a long time it has been known that women subject to mental, emotional or physical stress may experience temporary delay in menstruation[12,13]. It has also been shown that this type of amenorrhea can be relieved promptly by the administration of parasympathomimetic drugs[11]. Much of the mechanism underlying this peculiar type of amenorrhea as well as the mechanism of its relief by cholinergic compounds remains unexplained, although the evidence seems to indicate that the autonomic nervous system is involved. The relationship of stress to the parasympathetic nervous system is well known, but the connection between this system and menstrual bleeding is not clearly understood.

Uterine hyperemia is an integral part of the estrus phenomenon in women[11]. Kaiser[6] has shown that the administration of estrogen to experimental animals results in pronounced hyperemia of the endometrium. It also results in an increase in the interstitial acetylcholine content of the uterus[7]. It seems reasonable to assume that this hyperemia is secondary either to the vasodilating action of acetylcholine or conceivably to a relative diminution of the serum cholinesterase level[3]. Since prior administration of atropine temporarily inhibits this hyperemic response to estrogen, many observers have felt that it was mediated through the parasympathetic nervous system[4]. This thesis is particularly attractive in view of the known presence of cholinergic fibers in the uterus[10]. However, it should be noted that this same hyperemia occurs in ocular transplants of endometrial tissue which are devoid of nervous elements[8].

Soskin, Wachtel and Hechter[11] were the first to demonstrate clinically that bleeding could be produced in certain instances of delayed menstruation by the administration of a parasympathomimetic compound to potentiate the vasodilating effect of acetylcholine through inactivation of the enzyme cholinesterase. They were also first to conceive of this reaction as a diagnostic test for pregnancy and to show that such treatment did not interfere with or disturb an existing gestation. Their work has since been amply corroborated.

The prompt onset of bleeding in non-pregnant women and the absence of this response in pregnancy with the use of cholinergics constitute an economical, highly accurate test for pregnancy that can be done as an office procedure. As a therapeutic measure in simple delayed menstruation it is ideal, since many women, even though informed that their biological test for pregnancy is negative, will not be psychologically at ease until menstruation is reestablished.

In view of these considerations the present study was undertaken for the purpose of evaluating the efficacy of a new cholinergic preparation, Stigmo-

nene Bromide*, as a treatment for simple delayed menstruation and a diagnostic measure for early pregnancy.

Stigmonene Bromide [1-Benzyl-3-(Dimethylcarbamyloxy)-Pyridinium Bromide] is a synthetic alkaloid-like salt of the quaternary pyridinium series. Pharmacological investigations demonstrated that Stigmonene acts as an inhibitor of the enzyme cholinesterase[9] and is less toxic than compounds of the physostigmine group. Clinically, in both prophylactic and therapeutic use it was not attended by side effects [1,2,5,14].

Clinical Material and Procedure. From among patients who presented themselves at the Gynecology Clinic of the Jersey City Medical Center, a total of 116 women complaining of delayed menstruation were selected for this study. Early in our work it became apparent that certain requirements stressed by previous writers had to be met if reliable results were to be obtained. These requirements are: 1) no menstrual irregularity prior to the present complaint; 2) no evidence of the menopause; 3) no organic pelvic disease; 4) no causative endocrine or constitutional disturbance.

Of the original 116 patients, 100 met the aforementioned requirements. The remaining 16 patients in addition to their original complaint showed evidence of either organic pelvic disease, endocrine dysfunction, or the menopause. However, they have been included in this report to emphasize the importance of observing the limitations of the test.

Each patient's diagnosis was based on a carefully taken history, physical examination and pelvic examination. All women were given the Aschheim-Zondek test (Friedman modification) for pregnancy. Each patient received an intramuscular injection of 1 cc. of a 1:1000 solution (1 mg.) of Stigmonene Bromide on each of 3 successive days. If the menstrual flow was reestablished with the first or second injection, further treatment was discontinued. On the other hand, a patient was presumed to be gravid if no bleeding ensued after the third injection. All participants were informed of the possible effects the treatment might produce and were instructed to report the start of the menstrual flow or any symptoms of drug reaction.

Results. In a group of 100 patients who met the requirements for the test and who received 1 mg. of Stigmonene intramuscularly in 1 cc. doses on each of 3 successive days, the drug did not evoke the menstrual flow after the third and last injection in 83 instances (Table 1). These women were therefore considered to be gravid. The average number of days overdue in this group was 28.3. The diagnosis of pregnancy was established clinically in each of these cases. In all but one instance pregnancy was confirmed by the Aschheim-Zondek test (Friedman modification). This patient, whose clinical pregnancy was established beyond doubt by the presence of fetal heart sounds, had a biological test for pregnancy that was performed 43 days after her last menses and was reported as negative.

It was necessary in 4 instances to repeat the Aschheim-Zondek test in order to reconcile the results with those obtained by the single course of 3 Stigmonene injections and the clinical evidence of pregnancy, although these women were overdue from 3 to 8 weeks. The Stigmonene-diagnosed pregnancies proved to be 100% accurate in the group of 83 patients who met the requirements of the test.

Of considerable importance was the lack of deleterious effect on the gestation by the administration of Stigmonene. One patient in this group had an admitted self-induced abortion and 1 had a spontaneous abortion 21 days after receiving the last injection. In the latter case it was felt that in view of the time interval between the injections and the spontaneous emptying of the uterus, no causal relationship could be established.

* Stigmonene Bromide was supplied through the courtesy of William R. Warner, Division of Warner Hudnut, Inc., New York, Los Angeles, St. Louis.

Of the 17 remaining cases in the series, 16 who were amenorrheic for an average of 20.1 days, were considered not pregnant clinically. These had negative Aschheim-Zondek tests and bled in from 2 to 120 hours following the last injection (Table 1). The majority (88.2%) menstruated within 96 hours. The remaining patient in this group was first seen when her menses were 13 days overdue. Pelvic examination revealed a third degree retroversion of the uterus. It was also slightly enlarged and boggy. Three injections of Stigmonene were given. Ten days later an Aschheim-Zondek test was reported as negative but no bleeding had occurred. An Aschheim-Zondek test repeated 12 days later was reported as positive and the following day bleeding began and continued for 3 days. Subsequent pelvic examination was normal except for a persistent third-degree retroversion of the uterus. Whether the patient was originally pregnant and the biological test in error or whether she became pregnant later and the Stigmonene test was in error we are unable to state definitely. But we considered her as non-pregnant and the Stigmonene test in this instance a failure. Nevertheless, the efficacy of Stigmonene as a therapeutic measure in this series of 17 cases reached 94.1%.

The number of cases in this group of non-pregnant women is not sufficiently large to make any statistical conclusions as to the length of time required to establish menses or the relationship of this interval to the duration of the previous amenorrhea. A greater number of cases in this group would undoubtedly present a more well defined picture of the efficacy of Stigmonene in the treatment of simple delayed menstruation.

The results in the group of 16 patients who did not meet the previously mentioned requirements for the Stigmonene test, that is, the patients with irregular menstrual history, endocrine dysfunction and other chronic diseases, are presented in Table 2.

Eight of these women were found to be pregnant by clinical standards and by biological test. Six of these 8 showed a "positive" (failed to bleed) Stigmonene reaction, while 2 bled following the last injection in 24 and 72 hours respectively. One of these 2 proved to have an unruptured tubal pregnancy that was later removed at laparotomy and 1 bled moderately with cramps at the time of her second missed period. This patient was treated as a threatened abortion and successfully carried her pregnancy to term.

Of the 90 women with intrauterine pregnancies who received the Stigmonene test, 1 had a self-induced abortion, 1 a spontaneous abortion, and 1 showed symptoms of a threatened abortion. It is felt the incidence of

TABLE 1.—CLINICAL DATA AND RESULTS OF STIGMONENE TEST IN 100 AMENORRHEIC PATIENTS WITH NORMAL GYNECOLOGIC HISTORY PRIOR TO PRESENT COMPLAINT

	Number of Cases	*Age Range (years)*	*Average Days Overdue*	*Clinical Confirmed Pregnancy*	*Stigmonene Diagnosed Pregnancy*	*Stigmonene Elicited Flow*	*Aschheim-Zondek Test*	
							positive	*negative*
Pregnant	83	13–41	28.3	83	83	0	82	1
Non-pregnant	17	21–43	20.1	0	0	16 (in from 2 to 120 hours after last injection)	1*	17*

* One case presented different Aschheim-Zondek interpretations in a 12-day interval.

abortion in this group is comparable to that which would be encountered in any equal group of pregnant women.

In the non-pregnant group of 8 women in the series of 16 patients who did not meet the requirements for the Stigmonene test, 5 nevertheless showed a "negative" reaction, while 3 individuals failed to bleed after the third injection. Of these, 2 had menstruated irregularly for some time and were treated with cyclic therapy, while the third patient was admitted to the hospital with a diagnosis of tubo-ovarian abcess.

TABLE 2.—CLINICAL DATA AND RESULTS OF STIGMONENE TEST IN 16 AMENORRHEIC PATIENTS WITH IRREGULAR MENSTRUAL HISTORY, ENDOCRINE DYSFUNCTION AND OTHER ORGANIC DISEASES

	Number of Cases	*Age Range (years)*	*Average Days Overdue*	*Clinical Confirmed Pregnancy*	*Occurrence of Bleeding*	*Absence of Bleeding*	*Aschheim-Zondek Test*	
							positive	*negative*
Pregnant	8	16–39	27.5	8	2	6	8	0
Non-pregnant	8	20–36	23.1	0	5 (in from 6 to 120 hours after last injection)	3	0	8

These 16 cases serve to illustrate the fact that the requirements of the test must be met if accurate results are to be obtained.

In no instance was sensitivity to the drug observed nor were any untoward reactions noted.

Summary and Conclusions. 1. The rationale of the employment of cholinergics in the treatment of simple delayed menstruation and in the diagnosis of early pregnancy is discussed.

2. The requirements for the applicability of cholinergics in these circumstances are listed.

3. Data on the use of Stigmonene Bromide, a new cholinergic, in 116 patients with amenorrhea due to pregnancy or other causes is presented.

4. The Stigmonene Bromide test for early pregnancy proved to be both highly accurate and harmless to gestation.

5. Preliminary investigation of the use of Stigmonene Bromide in the treatment of simple delayed menstruation indicates that the drug is effective if certain discussed limitations are observed.

6. No instance of drug reaction or sensitivity was encountered.

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TREATMENT OF RHEUMATIC FEVER WITH ACTH

I. SMALLER DOSES OF ACTH IN ACUTE RHEUMATIC FEVER

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SINCE the original observations of Hench, Slocumb, Barnes, Smith, Polley and Kendall[3] on the effectiveness of adrenocorticotropic hormone (ACTH) in the acute phase of rheumatic fever, other writers have reported findings in corroboration of this effectiveness. Hench, as well as Wilson and Helper[14], McEwen *el al.*[5], Massell *et al.*[4] and Thorn *et al.*[13] reported on a group of selected cases, the results of which were comparable. They found that fever, arthritis and skin lesions disappeared promptly and that signs of carditis disappeared at an accelerated rate. This paper is the first of several to dwell upon the value of ACTH in cases of rheumatic fever of various degrees of severity and chronicity. Specifically this paper will dwell upon the use of small doses of ACTH in a carefully selected group of patients with a less severe type of the disease. This first study, begun in October 1949, was deliberately designed to use small doses mainly because of the natural conservatism that is associated with the advent of any new drug, especially a drug whose action is not entirely known. Another motive which prompted the use of smaller doses was the prevailing rationale that smaller increments of ACTH might encourage the adrenal cortex to accomplish some intrinsic hypertrophy. This theory, however, was unfounded and of course impossible to substantiate. The choice of patients in this initial study was deliberately aimed at avoiding any of the so-called complicated or severe cases. Chronic rheumatic fever and those in congestive heart failure were avoided. A subsequent report will deal with a larger group of rheumatic fever patients accepted for therapy without selectivity insofar as severity or chronicity is concerned.

Methods and Materials. Twelve cases were therefore selected for treatment with ACTH because they exhibited unequivocally the criteria for the diagnosis of rheumatic fever. The patients for this study were chosen on the basis that they presented at least two of the major plus two of the minor criteria. The major criteria established for this study were 4 in number, namely, carditis, polyarthritis, subcutaneous nodules and erythema marginatum. The manifestations of the minor criteria upon which selection was made were fever, elevated sedimentation rate, history of rhe-

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matic fever, serological evidence of preceding streptococcal infection and prolongation of the P-R interval. None of the cases had chorea. Thirteen other cases were omitted from this study because they failed to meet the unusually strict criteria for diagnosis. Of the 12 cases accepted for this study 6 patients were in the first week of the acute phase of their illness and 6 were in the fourth to eighth week of their illness. The latter were treated because of a poor response to salicylates and they were included in this study because their response to ACTH did not differ appreciably from that of the other group. Ten of the 12 patients were under 20 years of age. Eight were males and 4 females. In 6 of the cases this was the primary attack, in 5 the second attack and in 1 case the third attack.

The adrenocorticotropic hormone* used in this study was well controlled and assayed after the method of Sayers *et al.*[10]. The dosage of adrenocorticotropic hormone was decided arbitrarily as 0.4 mg. per Kg. of body weight per day. This dose was divided into 4 equal portions and administered intramuscularly every 6 hours. The dosage averaged 5 mg. every 6 hours for the children and 6 mg. every 6 hours for the adults.

Treatment was withdrawn abruptly in 10 of the patients when the sedimentation rate had declined to 30 mm. in 1 hour. In the remaining 2 cases it was withdrawn slowly. White blood counts and eosinophil counts were done at daily intervals during the first week and three times a week subsequently. For the latter study the method of Randolph[7] was employed. Sedimentation rates were done with Westergren tubes and read at 1 hour. Blood was drawn for the eosinophil count, sedimentation rate and white blood cell count 6 to 12 hours after the last dose of ACTH. Electrocardiograms were done daily on those patients who showed abnormal tracings and at appropriate intervals on all others. After release the patients were observed bimonthly and later monthly in the cardiac clinic. The duration of therapy varied from 4 to 32 days with a mean of 20.5 days. Ten of the 12 patients were treated between 18 and 22 days.

Results. The response to the ACTH of the major criteria is shown in Table 1. Signs and symptoms of carditis were present in 8 cases. Gallop rhythm, which was present in 3 cases, disappeared in 7 days. One case with cardiac enlargement by fluoroscopy showed a diminution of the size of the cardiac silhouette in 4 weeks. Apical systolic murmurs in 3 patients diminished or disappeared during hospital observation. Old valvular disease was present in 4 cases. In 1 patient, a loud aortic diastolic murmur disappeared on the twenty-fifth day of observation.

TABLE 1.

Major Criteria	*No. of Patients*	*Time of Disappearance of Signs*
Carditis	8	7–28 days
Arthritis	10	1 day (9) 2 days (1)
Skin Lesions	3	1–7 days

Arthritis was present in 10 patients and disappeared dramatically in 9 patients within 24 hours. The remaining case responded to an increased dosage in 48 hours.

Skin lesions were present in 3 cases. One case with erythema marginatum exhibited a clear skin in 12 hours and during the first 2 weeks of therapy the lesion could be caused to reappear if one of the 12 hour doses was omitted. One patient had subcutaneous nodules which were diminished in size within 72 hours and could not be found after 1 week of therapy. The skin of 1 patient with erythema nodosum cleared remarkably in 24 hours and completely in 72 hours.

Table 2 illustrates the response of the manifestations of the minor criteria to the ACTH therapy. Fever which was present in 9 of the 12 cases was reduced to normal within 24 hours in 8 of the 9 cases. The remaining case required a 50% larger dosage of ACTH and his fever disappeared 12 hours after the dosage was increased.

* The ACTH in this study was supplied by the United Laboratories in Pasadena, California.

TABLE 2.

Minor Criteria	*No. of Patients*	*Time of Disappearance of Signs*
Fever	9	24 hrs. (8) 48 hrs. (1)
Tachycardia	12	48 hrs. (4) 2–4 wks. (8)
Elev. Sed. Rates	12	10 days (3) 3–4 wks. (9)
Leukocytosis	10	At End of Therapy
ECG Abnormalities	6	4–10 days

Tachycardia was present in 12 cases and persisted from 48 to 72 hours in 4 cases and from 2 to 5 weeks in 8 cases.

Initial sedimentation rates ranged from 60 to 103 mm. in 1 hour. They dropped slowly to normal over a 3 week period in 9 cases. In 3 patients the sedimentation rate dropped to 9 to 16 within 10 days.

The leukocyte count was above 10,000 per c.mm. in 10 cases. In 6 of these patients it fell below 10,000 during the first week of therapy, and rose to between 12,000 and 20,000 white blood cells per c.mm. during the remaining period of treatment with ACTH. In 2 cases, serial counts were inadequate. In the remaining 4, the leukocytes were below 10,000 throughout therapy. In all cases, the white blood cell count was below 10,000 after ACTH was discontinued. During therapy, the eosinophil count dropped or remained low during the first week and rose secondarily. There were 2 distinct exceptions to suppression of the eosinophils during therapy. They were the 2 cases illustrated by Fig. 2. In this instance the eosinophil count rose before the cessation of therapy.

Fig. 1 is a representative case of the uncomplicated group. It demon-

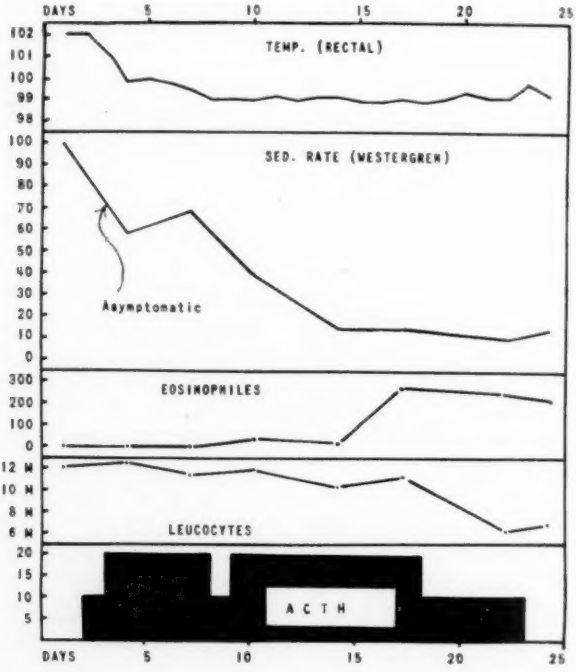

Fig. 1.—Response of acute rheumatic fever to ACTH.

strates the tendency noted in the majority of cases for the leukocyte count to remain sustained throughout therapy and its noticeable decline on the withdrawal of ACTH. The phenomenon was a consistent finding. Also illustrated in this particular case is the gradual rise noted in the eosinophil counts and the sustained higher levels of these counts even after discontinuance of ACTH.

Table 3 represents the initial eosinophil and leukocyte counts taken in all the patients proposed for therapy with ACTH. These patients were divided roughly into the 3 categories noted in Table 3, namely, those acutely ill and febrile, those afebrile but having objective signs of rheumatic activity such as increased sedimentation rate and prolongation of the P-R interval, and lastly those with elevated sedimentation rate only. It is notable that for the most part those cases with the smaller initial eosinophil counts had the highest leukocyte counts. This group fell almost uniformly under the category of those patients acutely ill and febrile. Conversely those patients who exhibited only elevated sedimentation rates showed higher eosinophil counts initially as well as lower leukocyte counts. The third group fell roughly in between the two aforementioned groups.

The electrocardiogram was abnormal in 6 cases. Abnormalities varied from prolonged P-R interval to third degree heart block. There were no abrupt changes in the electrocardiogram which could be specifically attributed to ACTH. All the abnormalities reverted to normal within 1 to 2 weeks.

Toxic Symptoms. One 8-year old girl receiving 20 mg. of ACTH daily developed hyperkeratosis pilaris. No other untoward symptoms were noted, such as weight gain, moon-face, acne or hirsutism.

TABLE 3.—INITIAL COUNTS TAKEN ON CANDIDATES PROPOSED FOR THERAPY WITH ACTH LISTED ACCORDING TO THEIR CLINICAL STATE

Patients Acutely Ill and Febrile		*Patients Afebrile but Having Objective Signs of Rheumatic Activity*		*Patients with Elevated Sed. Rate Only*	
Eosin./cmm	*WBC/cmm*	*Eosin./cmm*	*WBC/cmm*	*Eosin./cmm*	*WBC/cmm*
255	11,300	274	7,950	187	6,950
33	10,700	22	11,300	198	10,600
0	14,200	55	7,200	198	9,000
0	12,150	100	10,250	166	9,400
0	14,600	300	7,450	198	6,100
33	11,250	22	8,750	61	5,500
33	27,800			272	9,150
11	22,600			161	7,150
143	13,700			205	11,200
				233	6,150

Relapse. No true relapses have occurred in any of our cases after therapy was stopped. In 3 patients after therapy was discontinued, the sedimentation rate climbed rapidly, reaching previous levels in 4 to 7 days. Joint pains and tachycardia recurred in 2 of these patients. Treatment was reinstituted at the previous dosage after which the sedimentation rate and all signs returned to normal in 9 to 10 days.

Figure 2 represents the phenomenon just described. This is a case of a 13-year old female with previous rheumatic heart disease, and considered the most severe of the group. It will be noted that her response to the initial

dosage of ACTH was properly dramatic. On withdrawal of the ACTH with the return of the sedimentation rate to normal a so-called "rebound" phenomenon was noted with a rise of the sedimentation rate and return of symptoms. Reinstitution of ACTH therapy promptly resulted in a loss of symptoms and a return of the sedimentation rate to normal within 10 days. It is notable that the 2 patients exhibiting this rebound phenomenon were clinically considered to be relatively severe cases of active rheumatic fever.

Discussion. Since the pathologic physiology of rheumatic fever is still obscure, the rationale supporting the use of ACTH remains empirical. The eosinophil response has been reputed to be the most sensitive known gauge of the release of cortical steroids[2]. This was the only primary physiological effect of cortical hormones which could be followed in this study. Repeated eosinophil counts gave adequate proof that even small doses of ACTH were effective in releasing a cortical response. However, such small doses were used on a selected group of cases which were admittedly acute and "less severe." Also care was taken to avoid inclusion of such cases that might show evidence of congestive heart failure, because of the difficulties surrounding the control of such patients in a large institution. The effectiveness of small doses of ACTH, while established, is admittedly

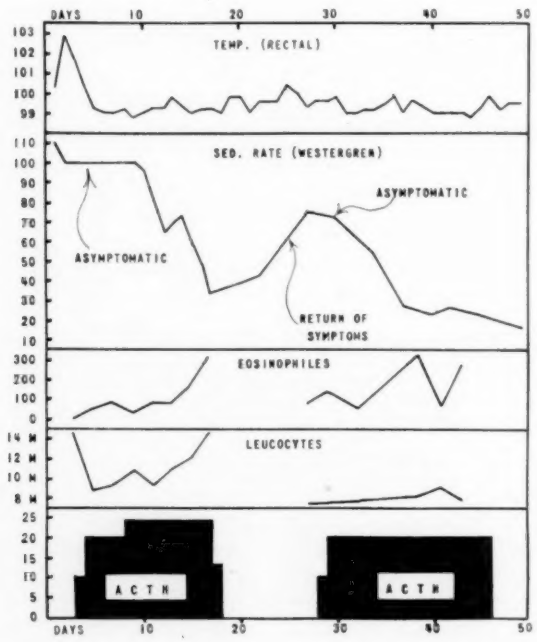

FIG. 2.—ACTH response with "rebound" phenomenon.

PROGRESS. All of these patients have been observed over periods varying from 14 to 22 months. To date, all patients without exception are in the quiescent phase of rheumatic fever and have no evidence of newly acquired valvular disease or aggravation of preexisting valvular disease.

inadequate for treatment of cases which might be classified as "moderately severe" or "severe." The case indicated by Figure 2 attests to the inadequacy of smaller doses of ACTH and of brevity of treatment in a moderately severe case of rheumatic fever.

There is no existing explanation for the effectiveness of ACTH in rheumatic fever. Certain theories have been set forth to support its use, all of which are still unfounded at the present writing. These theories state that ACTH acts: (a) by interference with the release of the anaphylactogenic substance of the faulty antigen-antibody reaction[1], or (b) by an alteration in tissue permeability through inhibiting the action of hyaluronidase[6,11], or (c) by inhibition of the development of granulation tissue by suppression of the fibroblastic reaction in the mesenchymal tissue[8], or (d) by the production of hypercorticism[9], or (e) by a blocking action similar to that seen in the Schwartzman phenomenon[12]. The eosinophil count described at the initial phase of the disease would seem to indicate a proper cortical response in the patients. Ostensibly this response may have been quantitatively or qualitatively inadequate and the added exogenous supply of ACTH may have produced the necessary hypercorticism. The response to ACTH in the 1 case in Figure 2 showing eosinophil rise before cessation of therapy very likely indicated inadequate therapy. This was further verified by a return of signs and symptoms in this instance.

The primary aim in the treatment of rheumatic fever is the prevention of crippling heart disease. There is no indication at the present writing that ACTH can accomplish this particular aim. Much longer periods of observation and a much larger number of patients will be necessary before any such conclusion can be reached.

Summary. 1. ACTH is an effective agent in the treatment of the acute stage of rheumatic fever. Small doses were found to be effective in those cases which may be classified clinically as acute and "mild." Under therapy the signs and symptoms were noted to disappear at an accelerated rate. Fever, arthritis and skin lesions disappeared rapidly and completely. Some of the signs of carditis cleared rapidly while tachycardia persisted from 2 to 4 weeks.

2. The white blood cell count rose during treatment and declined abruptly at cessation of therapy. The eosinophil count tended to be low before therapy, remained low during therapy and returned to normal levels following therapy. The 2 cases inadequately treated showed return of eosinophil levels to normal before cessation of therapy.

3. Small doses of ACTH as well as short duration of treatment were found to be inadequate for the treatment of moderately severe active rheumatic fever.

4. ACTH appears to lessen the inflammatory reactions and suppress the signs and symptoms of disease. While it cannot be said to cure the disease, it definitely does shorten the course of it. It is likely also that its suppressive action is at work while the disease runs its natural course.

5. While it is hoped that ACTH may be effective in the prevention of crippling heart disease, no such conclusions can be drawn at the present time.

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TREATMENT OF RHEUMATIC FEVER WITH ACTH
II. ACTH BY THE CONTINUOUS INTRAVENOUS DRIP METHOD

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In the initial report by this group[10], reference was made to the intermittent intramuscular injection of ACTH in cases of acute rheumatic fever. While the responses noted were in keeping with the gratifying results reported by others[1,3,4,5,6,7,8,11,12,13], certain facts must be elucidated to explain subsequent reports which may not altogether be consistent with the previous one in terms of dosage and results.

This work had its origin in late 1949 at which time caution was certainly the keynote in the use of this hitherto untried drug. Conservatism was doubly indicated in this drug to which was attributed many deleterious side effects and complications, most of which were exaggerated. In this earlier report, then, the caution was exercised in the form of: (a) deliberate omission of cases other than the acute form of rheumatic fever, and the avoidance of any cases complicated with heart failure or very severe carditis, and (b) the use of extremely small doses of ACTH. This type of investigative method could only give a narrow expression of the values of ACTH in one of the "types" of rheumatic fever. In retrospect, the success of the treatment with smaller doses of ACTH by intramuscular injection must be related to the choice of cases for one individual study.

This paper, in contrast, is a preliminary expression of the results noted by ACTH therapy in 37 consecutive cases of rheumatic fever. All cases were accepted without regard for severity, chronicity, or the presence of congestive heart failure. In this series 3 methods of therapy were employed: (a) higher doses of ACTH administered by intermittent intramuscular injection, (b) small doses of ACTH by slow continuous intravenous drip, and (c) the consecutive use of both of these methods.

The need for a higher dose of intramuscularly administered ACTH (100 mg. daily) became immediately apparent when the more protracted cases failed to respond to the smaller doses which proved so effective for the acute form of rheumatic fever. Figure 3 is illustrative of this phenomenon. The clinical response in this case of severe, chronic rheumatic fever with congestive heart failure was not effected until the dosage of ACTH was raised

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to 100 mg. daily. It will be further noted that an attempt to revert to a lower dose of ACTH resulted in a "rebound" which was again amenable to increased dosage of ACTH.

The need, then, for both larger doses of ACTH and for longer periods of treatment created a serious problem of drug supply for institutional care where as many as 15 cases were being treated simultaneously. For this reason word of the possibility of intravenous use of small doses of ACTH was received with enthusiasm. Sayers[9] gave large doses of ACTH intravenously over a half-hour period, to note that it rapidly disappeared from the blood stream. Gordon[2] reported that the administration of small doses of ACTH by continuous intravenous drip method resulted in a steady sustained stimulation of the adrenal cortex.

Figure 1 illustrates the remarkable eosinopenic effect from intravenous injection of small doses of ACTH. Curve number (1) indicates the effect from 5 mg. of ACTH diluted in 10 cc. of normal saline when given intravenously to a normal subject within 2 seconds. The immediate drop in circulating eosinophils is in evidence after 30 minutes. Curve number (2) represents the effect in the same individual from the identical dose given intra-

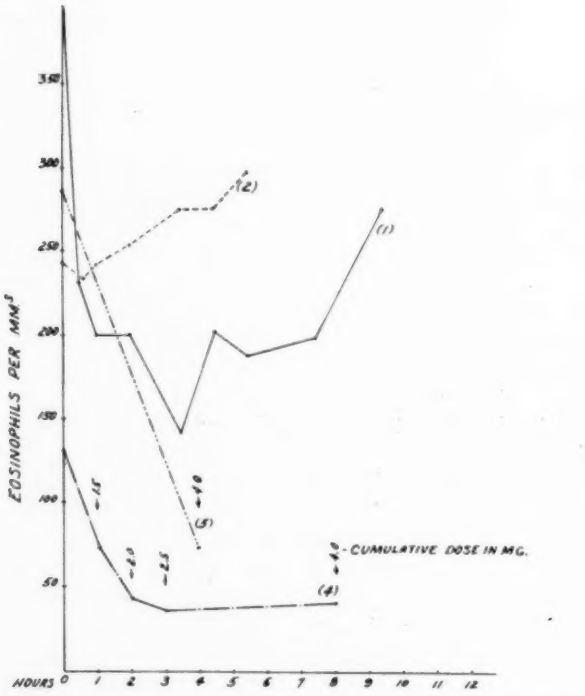

FIG. 1.—The effect on circulating eosinophils from intravenously and intramuscularly administered ACTH.

muscularly. There is no eosinopenic response. Curve numbers (3) and (4) show the eosinopenic response after the ACTH is given by the slow intravenous drip method. A satisfactory drop in circulating eosinophils is observed after infinitesimal amounts of ACTH have been infused. In curve number (3) there was a change of from 285 to 65 eosinophils per mm. within 4 hours[11]. This change required only 4 mg. of ACTH. In curve number (4) a similar effect is noted within 3 hours from 2.5 mg. of ACTH.

Method of Treatment. The ideal method of administration would have been to maintain an infusion over a 24-hour period for days on end without interruption. This is possible only in adults and would necessarily require modification in the handling of children.

Our method proved satisfactory when the total daily dose (10 to 20 mg.) was dissolved in 1 L. of 2.5% glucose in distilled water to which was added 10 mg. of heparin. Originally a solution of 5% glucose in water was used. This caused a complication of localized thrombophlebitis in 2 cases. There were no further complications noted after the solution was changed to 2½% glucose and heparin was added. The children offered little resistance to the intravenous method. Freedom of movement was possible in most cases while the infusion was in place. Also of psychological help was the grouping of all the pediatric cases in 1 room.

The advantages of the intravenous drip method were:

(a) Markedly reduced drug costs, since the requirements were approximately one-tenth of that required by the intramuscular route.

(b) More rapid effect as reflected in the appearance of the signs of Cushing's syndrome. It was our general impression that patients treated with intravenous ACTH developed Cushing's syndrome more rapidly than those receiving larger doses intramuscularly.

(c) Eosinopenic response to ACTH could be noted at any time during the infusion.

The disadvantages noted were:

(a) Rare occurrence of thrombophlebitis which was amenable to the change of solution as described above and the addition of heparin.

(b) The usual "vein difficulty" encountered in children after weeks of venipuncture whenever the pediatric patients required very long periods of therapy. The intravenous method in situations of this kind may have to be abandoned in favor of the intramuscular method.

(c) In the pediatric cases the 24-hour continuous infusion was impossible because of the impractibility of fixing the extremity during sleep. A compromise time of approximately 14 to 16 hours continuous infusion per day was found to be tolerated by the children.

Evaluation of Treatment. The effect of ACTH administered by slow intravenous drip on active rheumatic fever is graphically demonstrated by Figure 2. Symptoms of arthralgia were promptly relieved within 4 hours. Fever and signs of arthritis disappeared in 24 hours. All evidence of carditis disappeared on the 15th day of treatment. The sedimentation rate began its decline after 1 week of therapy and returned to normal values on the 11th day of therapy. Signs of Cushing's syndrome first were in evidence on the 10th day, increased on the 19th day of treatment, and began to regress 10 days after treatment was completed.

A comparative study between the intramuscular and intravenous administered ACTH is shown by Figure 3. This was a case of severe rheumatic

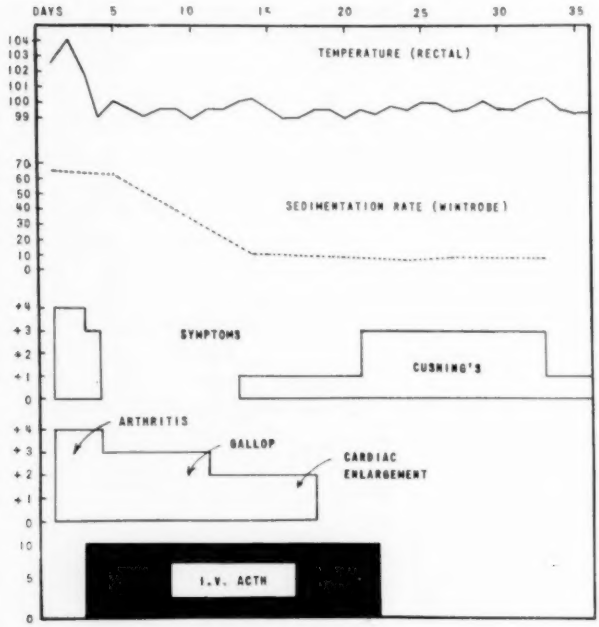

FIG. 2.—Graphic demonstration of response of a case of acute rheumatic fever treated by 10 mg. ACTH daily for 20 days by slow intravenous drip method.

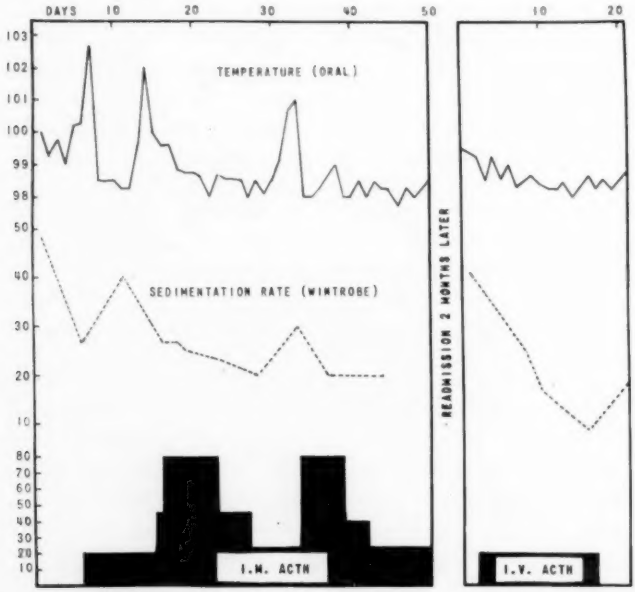

FIG. 3.—Comparative results between intramuscularly and intravenously administered ACTH in the same patient.

fever with congestive heart failure. The initial dosage of ACTH by intramuscular route was obviously small by present standards, and hence does not lend itself to fair comparisons. Still the effect by the intramuscular method is noteworthy. It will be seen that as the evidence for rheumatic activity increased an increment in the amount of intramuscular ACTH proved ineffective in suppressing this activity. Two months later in a subsequent admission with obvious recrudescence of rheumatic activity the daily intravenous infusion of 18 mg. ACTH daily was at least equally effective in suppressing the signs of rheumatic activity.

Results of Treatment. Thirty-seven cases of active rheumatic fever have been treated with ACTH since the first report. The problem of trying to tabulate the results of treatment by table or graph with mathematical deductions is discouraging in a disease of so protean a nature and with such diversification of results. Before such tabulations will be attempted, more cases and longer periods of time are required. Especially is this true when selectivity of cases is avoided. At some future writing such a tabulation may prove feasible.

Broadly speaking, results are noted from this study which can be stated as follows: All cases of *acute* rheumatic fever have responded to ACTH therapy promptly and satisfactorily without recurrences. Five cases of the chronic or polycyclic type of rheumatic fever, while showing a suppressive effect on initiation of therapy, have all shown recrudescence after therapy. There was 1 case that showed no response whatever to ACTH by intramuscular or the intravenous method. This case was subsequently found to have subacute bacterial endocarditis. Congestive heart failure, noted in 5 cases, proved to be no contraindication to therapy.

No definite relationship could be observed between the severity of the disease and the rapidity of response. There was some relationship noted between the duration of rheumatic activity prior to treatment and the length of time required for treatment. This relationship may have been more apparent than real owing to the great difficulty in establishing the time of onset of the rheumatic fever.

Another observation of dubious value is related to the time of appearance of signs of Cushing's syndrome. In the case of subacute bacterial endocarditis, showing no response to ACTH, Cushing's syndrome was never in evidence in spite of large doses. With this one exception, signs of Cushing's syndrome were produced in every case and were reversible in each instance[5,11,12].

Conclusions. 1. The method of administration of ACTH by continuous or interrupted intravenous drip was found to be both practicable and efficient.

2. Response of adrenocortical activity as noted by onset of Cushing's syndrome and eosinopenia was thought to be accelerated by the intravenous drip method.

3. The effectiveness of ACTH in acute rheumatic fever is again observed. Treatment is advised as early in the disease as is possible.

4. Recrudescence was noted in 5 cases; all of which could be classified as the chronic or polycyclic type of rheumatic fever.

5. ACTH action must still be considered as suppressive rather than curative.

Grants from the Los Angeles County Heart Association and the 20-30 International Rheumatic Fever Foundation through the American Heart Association are gratefully acknowledged.

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AIR POLLUTION AND COMMUNITY HEALTH

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That Community Health is an important aspect of the air pollution problem is finally beginning to receive the attention it deserves from Industrial and Public Health physicians and engineers here in America. After the publication in 1948[10] of our paper, "Health Costs of Urban Air Pollution," and especially following the Donora disaster of 1948[8], workers in these fields actively denied, in one symposium after another across the country, the existence of any valid evidence that community health was involved. Within the limits of our meager research funds, we have attempted to collect such evidence through the past decade, and it is the purpose of the present communication to present further significant findings obtained by more detailed study of the smoke-health relationship in Chicago.

That American Industrial and Public Health authorities are about ready to abandon their obstructive negative interest in favor of a constructive positive one, is evidenced by two recently published items. On January 17, 1952, the American Medical Association's Council on Industrial Health authorized its Committee on Environmental Health, Hygiene and Safety" to undertake a critical evaluation of the literature dealing with the health or medical aspects of atmospheric pollution"[1]. This council action was preceded by an article from the Harvard School of Public Health on "The Epidemiology and Social Significance of Atmospheric Pollution" published a few months earlier, in which the authors said[7]:

"The case against smoke stands or falls by its effects on the respiratory system. . . . If it is admitted that severe smoke pollution can be one of the causes of death from respiratory disease (as at Donora), then it follows reasonably that lesser degrees of pollution are likely to cause pathological results of less severity."

British authorities had been interested in the problem's community health aspects for many years. Russell in 1924[11] wrote:

"Whenever the scavenging of the air is interrupted by calms, so that smoke products accumulate . . . we move about choking, our eyes irritated, our faces grimy. . . . It is then that our pulmonary mortality is run up and the death rate of the year determined."

Langrishe, Lecturer on Public Health at the University of Edinburgh, said in 1935[5]:

"Statistics show a close relation between death rates and atmospheric conditions. The numbers of deaths from pulmonary and cardiac diseases increase in direct proportion to an increase in the intensity and duration of smoke fogs. At the extremes of life these effects are most marked. . . . There is also good ground for believing that the tarry matter of smoke is at least partly responsible for the increase in cancer of the lung."

And in 1947, Galloway[3] wrote that:

"It is fair . . . to say that there is sufficient silica, carbon, tar and sulfur dioxide in the air of most industrial areas to cause some degree of pulmonary fibrosis, to irritate the respiratory mucous membranes, and to predispose to respiratory disease."

Foulger[2], an authority on Industrial Health in America, wrote in 1949:

"We are concerned here with assessment of the health hazard which may exist more or less continually in large industrial areas such as Los Angeles or Chicago. . . . The fortunate rarity of acute incidents such as

those in the Meuse Valley and at Donora must not delude us into thinking they are in a class apart. Actually, from the physiological point of view, they are mere magnifications of a frequent pattern. . . . The true test of health hazard to the general public from any particular atmosphere is the ability of this atmosphere, when inhaled, to produce physiological deterioration in exposed persons, and especially in those having respiratory or cardiac diseases. No degree of "cleaning up" of our cities can be considered satisfactory from the medical point of view unless it results in an atmosphere the breathing of which imposes no physiologic load upon the least resistant inhabitant, the sufferer from respiratory or cardiovascular disease. . . ."

Logan[6] in 1949 demonstrated the very sharp rise in deaths from respiratory and cardiac causes during and immediately following a severe 5-day smog in London, with an excess of more than 300 deaths over and above the number normally to have been expected in the 3-week period studied. We also showed[9] a sharply significant rise in the number of such deaths during severely smoggy periods in Los Angeles from 1946 to 1949. These evidences of the more acute effects upon persons already ill from cardiac and respiratory diseases receive further substantiation from our Chicago survey reported in 1948[10], in which we show direct correlation between amount of sootfall and death rates for tuberculosis, pneumonia and respiratory tract cancer in the city's contrasting cleanest and dirtiest areas.

There is now offered a more detailed analysis of these Chicago statistics, using death rates specific for age, sex, and color. Such refinements of the statistical study bring out certain addi-

TABLE 1.—AGE SEX SPECIFIC DEATH RATES FOR PNEUMONIA AND RESPIRATORY TRACT CANCER IN CHICAGO (WHITE RACE ONLY)

Age Group	Cleanest Community Areas 1–4, 9–21, 72–75		Ratio Males/ Females	Dirtiest Community Areas 8, 26–28, 31–39, 59–61		Ratio Males/ Females	Area 28 Only Males	Area 32 (Loop) Only Males	Ratios of Rates for Dirtiest Area/ Cleanest Area	
	Males	Females		Males	Females				Males	Females
Pneumonia Death Rates per 100,000 in Indicated Population Group per Year										
30–39	6 (12)	3 (7)†	2.00	38 (53)	10 (13)	3.80	100 (26)	* (2)	6.27	3.33
40–49	20 (37)	6 (12)	3.33	90 (121)	15 (17)	6.00	211 (65)	277 (10)	4.50	2.50
50–59	32 (43)	13 (17)	2.46	131 (154)	37 (21)	3.54	287 (36)	416 (14)	4.09	2.85
60–69	81 (52)	25 (19)	3.24	265 (170)	72 (36)	3.82	522 (84)	443 (10)	3.27	2.88
70–74	155 (26)	103 (23)	1.50	329 (54)	142 (21)	2.32	380 (16)	1311 (7)	2.22	1.38
75 & over	324 (50)	171 (39)	1.89	497 (63)	267 (37)	1.86	363 (11)	1050 (4)	1.53	1.56
30 & over	(220)	(117)		(615)	(145)		(238)	(47)		
Respiratory Tract Cancer Deaths per 100,000 in Indicated Population Group per Year										
30–39	* (4)	* (2)		4 (6)	* (1)			(0)		
40–49	18 (34)	9 (18)	2.00	20 (28)	6 (7)	3.33		(1)	1.11	
50–59	68 (91)	19 (25)	3.58	96 (113)	39 (19)	2.46		178 (6)	1.41	
60–69	165 (106)	38 (26)	4.34	252 (162)	46 (22)	5.48		266 (6)	1.53	
70–74	239 (40)	63 (14)	3.79	225 (37)	* (4)	*		(1)	0.94	
75 & over	246 (38)	66 (15)	3.73	211 (26)	51 (7)	4.14		(1)	0.86	
30 & over	52 (313)	15 (100)	3.41	76 (372)	16 (60)	4.81		119 (15)	1.46	
Population Numbers in Various Groups at Risk (taken from U. S. Census of 1940)										
30–39	63836	72612		47246	43374		8728	800		
40–49	61445	64425		46175	38548		10257	1204		
50–59	44602	43268		39205	19089		8468	1123		
60–69	21387	24955		21400	16639		5365	753		
70–74	5590	7421		5476	4917		1403	178		
75 & over	5142	7612		4242	4617		1010	127		
Total	202002	220293		163744	127104		35231	4185		

* Less than 5 deaths, rates not calculated
† Figures in parentheses indicate numbers of deaths in 3-year period

tional points of great importance in establishing the validity of community health hazards from polluted air.

While using the same basic soot-fall and mortality data as in our study reported in 1948[10], we now have classified the male-white and female-white pneumonia and respiratory tract cancer deaths by age decades from 30 years onward. This was done only for the cleanest and dirtiest blocked areas of the city, as indicated in the accompanying table, in order to obtain the sharpest possible contrasts.

Inspecting first the section of the table dealing with pneumonia deaths, we see that the death rate for this disease rises sharply in all categories with advancing age, that the death rate for men is always higher than for women, that the rates are always higher in the dirty areas than in the clean, and that the difference between pneumonia death rates for dirty and clean areas is greatest for the youngest age-decade studied, and lessens steadily on toward the old-age extreme for both sexes. The highest rates for every age decade are found among residents in the Loop area (No. 32) and almost as high in the adjacent area just to the west (No. 28). The significance of these findings will be discussed in a later paragraph in connection with other pertinent observations.

With respiratory tract cancer death rates the most significant point brought out by the age-specific rate calculations is the earlier age-onset of the astonishingly high male death rates among residents of the city's dirty areas. The very high death rates come on a full decade earlier in the dirty areas than in the clean, and it seems to be this earlier onset of high rates which largely accounts for the 46% higher total rate there. There seems to be no significant difference between clean and dirty areas in the final old-age rates attained, except possibly for a slight indication of exhaustion of the supply of cancer-susceptible individuals at older ages in the dirty areas.

Greatest significance attaches to the fact that the ratio of pneumonia death rates for men in the dirty districts and clean districts is highest in the 30 to 39 year age group and declines steadily on toward old age (from 6.27 at ages 30 to 39 down to 1.53 at ages 75 and over). In all likelihood this is associated with the greater physical activity of men in the earlier decades and a consequent inhalation of greater volumes of the dirt-laden air. As physical activity and volume of air breathed decline with advancing age, the pneumonia death rates of the dirty districts come down closer to those of the clean. With women the contrasts are less sharp but assume the same general pattern. Beyond age 75 this ratio of dirty to clean area rates is the same for both sexes.

In support of the likelihood of volume of air breathed being a major factor in dirty air damage, we may cite studies on experimental animals[13] living in beryllium tainted atmospheres. With only the minute air content of beryllium capable of killing 12% of the exposed animals in a given period of restful existence, enforced activity resulted in the death of all. We cannot experiment similarly with people, but their pneumonia death rates in clean and dirty air (as cited above) certainly indicate the likelihood that dirty air does indeed become more damaging the greater the amount inhaled and the more thoroughly the dirty air penetrates deep into the lungs. This can account not only for the sharpest contrasts between clean and dirty districts in the early age groups, but also for the consistently higher rates and ratios for men than women of all age groups.

These age-specific and sex-specific death rate studies in Chicago's clean and dirty districts are now being broadened to see whether socio-economic or occupational factors can account for much of the observed contrasts. Occupations carrying exposure to certain types of industrial dusts are known to increase respiratory disease hazards, hence this factor must also be evaluated in the Chicago picture. Even though an occupational relationship is found, however, we would only be providing further emphasis for the general respiratory hazards of breathing polluted air.

Our previous Chicago studies were criticized by the Harvard School of Public Health authors[7], who objected to the use of sootfall (dustfall) statistics as valid measures of prevailing air pollution, preferring instead data on some common pollutant such as SO_2 remaining in the air. Sulfur dioxide is indeed one of the most common pollutants of combustion and industrial sources, and today a few cities are keeping record of its concentration within their boundaries. Fortunately an extensive survey of SO_2 in the Chicago atmosphere[12] had been carried out only a few years before our respiratory disease study was made there, so let us see what relation such SO_2 data bear to those for sootfall.

For the Loop and downtown business district there was found an air SO_2 average of 0.40 ppm., and in the Congested South Side residential areas (31st to 48th Streets) an average of 0.27 ppm. In the cleaner outlying residential areas there was much less SO_2, the rough average being about 0.10 ppm. The SO_2 concentrations thus exhibit the same regional gradation from the Loop outward that is found with sootfall data, which ranged from 160 tons per square mile per winter month in the Loop down to 70 in the Congested South Side and on down to an average of 20 in the cleanest outlying residential districts. It is quite obvious, therefore, that the significant relationship we found to exist between sootfall and respiratory disease would also hold equally well for atmospheric SO_2.

In further support of our use of sootfall statistics as the most valid indication of degree of air pollution thus far available, we might cite their even more recent recommendation and use by Public Health Service investigators[4]. They, too, found a significantly higher incidence of respiratory infections in the high-sootfall portion of a Maryland city than in its cleaner districts. They failed to make any mention, however, of our earlier work which their methods mainly copied and their results supported.

The evidence is becoming increasingly clear that polluted air does indeed carry respiratory hazards of serious import. By its more acute effects in periods of dense smogs, it markedly increases life hazards for those individuals already handicapped by preexisting respiratory or cardiac troubles. Its more insidious effects through years of lesser exposure show up in a chronic respiratory irritation which predisposes to pneumonia and tuberculosis and brings on the high old-age rates for lung cancer a full decade earlier in life. Studies are badly needed to show just what air pollutants, singly or in combination, can produce such effects on the respiratory system through long-term continuous exposure. Such studies would differ sharply from those dealing with short-term in-plant worker exposures. Funds to cover such studies have been requested repeatedly from the U.S. Public Health Service and consistently refused.

Summary. Death rate studies (specific for age, sex, and color) for Chicago's most polluted and cleanest con-

trasting areas bring out the following pertinent findings:

The death rates for pneumonia rise sharply in all categories with advancing age, are always higher for male than for analagous sections of female populations, are always higher in the dirty areas than in the clean, and the difference between rates for the dirty and the clean areas are greatest for the youngest age-decade studied (30 to 39 years) and lessen steadily on toward the old-age extreme for both sexes. Highest rates for every decade are found among residents in the dirty Loop area and in the areas adjacent to it on the west.

With respiratory tract cancer death rates, the most significant finding is that the astonishingly high old-age male rates come on a full decade earlier in the most polluted sections of the city than in the clean. This earlier onset of high rates in the dirty districts seems largely to be responsible for the 46% higher total rate there. There seems to be no significant difference between clean and dirty districts in the final old-age rate attained, except possibly for a slight indication of exhaustion of the supply of cancer-susceptible individuals at the older ages in the dirty areas.

Regional differences of sootfall within the city of Chicago show fairly close correspondence with sulfur dioxide concentrations in the air. This gives added significance to our correlation studies in which soot-fall data were taken as the best index available of prevailing air pollution.

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EVALUATION OF VASODILATOR DRUGS IN FOUR PATIENTS WITH ARTERIOSCLEROSIS OBLITERANS*

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The effects of intramuscular or intravenous injections of pancreatic tissue extract on claudication time[2,6] and of various parenteral vasodilators on skin temperature have been studied[7,10,11,15]. Since, in long continued use of a drug, the oral route is much to be preferred, it was thought to be of interest to observe the effects of vasodilators which can be given by mouth on intermittent claudication, night cramps, claudication time and skin temperature. The following drugs were tested:

1. Pronestyl® (procaine amide) is the amide analogue of procaine. However, it is not destroyed by the esterase which splits procaine rapidly into para-aminobenzoic acid and diethylamino alcohol[9]. It does possess the trialkylamino group which is common to diethylaminoethanol, procaine and other compounds which have a spasmolytic effect on smooth muscle[5].

Preliminary studies of the effect of intravenous diethylaminoethanol in this laboratory have indicated an increased blood flow through the skin which did not occur after intravenous Pronestyl®. Recently Newman and Clark[14] reported that procaine amide has only one-fifth the vasodilator action of procaine in animals as measured by femoral blood flow.

2. Roniacol® (beta pyridyl carbinol tartrate), is the alcohol analogue of nicotinic acid and is believed to combine the vasodilator effect of alcohols with that of nicotinic acid[3]. Preliminary reports on its use clinically have been encouraging[3,16] and skin temperatures have shown significant rises following intravenous injection.

3. Priscoline® (benzyl imidazoline) is an adrenolytic agent which also blocks sympathetic vasoconstrictor impulses in higher dosage[1,8,11]. Skin temperature studies have shown increases in peripheral blood flow following intravenous administration[7,8,15]. Priscoline® has also been thought effective in the treatment of patients with impaired circulation[8].

4. SKF 688A (N-phenoxyisopropyl-n-benzol-B-chlorethylamine hydrochlo-

* The work described in this paper was supported in part by grants from the New York Heart Association and the Public Health Research Institute of the City of New York.

ride) is the n-phenoxyisopropyl ester of dibenamine. It has been noted to have adrenergic and sympatholytic properties similar to dibenamine and it is capable of producing extensive sympathoadrenal blockage following oral administration. It has been found to be much more potent than dibenamine[12]. In humans, preliminary studies have shown postural fall in blood pressure, miosis, vasodilatation, dizziness and antagonism to the excitatory action of adrenalin[12]. Other physiologic effects reported have included faintness, weakness, fatigue, diarrhea, drowsiness, headache, nasal congestion and blurred vision[13].

Methods and Material. Four male patients with clinical signs of arteriosclerosis obliterans were studied. The incidence of intermittent claudication and night cramps was listed and graded before and during the experimental periods.

The drugs and placebos were given orally for approximately 15-day periods in divided daily doses as follows: Pronestyl®, 2 gm.; Roniacol®, 600 mg.; Priscoline®, 300 mg.; and SKF 688A, 120 mg. A few additional experiments were also done with intravenous diethylaminoethanol, Dibenamine®, Roniacol® and Priscoline®.

Claudication time was measured twice weekly on a bicycle ergometer[17]. Two tests were carried out on each occasion with 10 to 15 minutes rest between them. Each patient rested for a similar period prior to the first test. All observations were made 3 to 4 hours after administration of the drug and the environmental conditions were maintained relatively constant. Two hundred and fifty-four ergometric tests were done on 4 patients.

Skin temperatures were recorded quasi-continuously over periods of 180 minutes in a constant temperature room at approximately 20° C and 50% humidity; the patients were in a fasting state. These recordings were done on 3 of the 4 patients toward the end of each experimental period.

Abbreviated Case Histories. MR was a 72-year old white male with generalized arteriosclerosis, diabetes mellitus, bilateral cataracts and chorioretinitis. Intermittent claudication had been present in his right calf for several years in addition to severe night cramps. Roentgenograms of the legs were negative for soft tissue calcification.

JK was a 64-year old white male with generalized arteriosclerosis, hypothyroidism, and bilateral cataracts. He had had claudication in his left leg on walking 1 block for many years and severe night cramps. Physical examination revealed a blood pressure of 190/70, an enlarged heart, and absence of all but the left femoral pulse in the legs. There were well marked postural color changes and moderate trophic changes. An ulcer with a large hyperkeratotic scab was present on the right lateral malleolus. Roentgenograms of the legs revealed marked bilateral calcification on the femoral and popliteal vessels.

VR was a 61-year old Negro male, born in Italy, with generalized arteriosclerosis and arteriosclerotic heart disease. He had had intermittent claudication and moderately severe night cramps for 3 years. There were moderate postural color changes with minimal trophic changes. The peripheral pulses were palpable and roentgenograms of the legs were negative for soft tissue calcification.

RA was a 50-year old white male with hypertension, generalized arteriosclerosis, portal cirrhosis, periarthritis of both shoulders. He had had intermittent claudication involving mainly the right leg for 5 years, without night cramps. He had occasional numbness in the right leg. Pulsations in the legs were diminished with absence of the posterior tibial pulse on the left. There were moderate postural color changes with moderate trophic changes and severe hyperhidrosis.

Results. The circulatory effects of the 4 drugs and their corresponding placebos are best considered separately.

1. Pronestyl® was given to 3 patients in dosage of 500 mg. every 6 hours, for approximately 14 days. An identical placebo was administered for the same period. With these relatively small doses there was no change in the incidence of claudication or severity of the night cramps or of exercise tolerance. Observations on skin temperatures were made during the period of oral Pronestyl® administration even though earlier studies[3] indicated that intravenous infusions of procaine amide had no effect on skin temperature. Two

patients (JK and MR) were given a second course of Pronestyl®. In none of the patients was there a significant rise in skin temperature.

2. Roniacol® was given in dosage of 200 mg. every 8 hours for approximately 14 days. Identical placebos were also given for a similar period. All patients noted improvement in their symptoms of claudication and those who suffered from night cramps were improved. The night cramps became much less frequent in 2 patients and disappeared completely in the third. Two patients had significant increases in their claudication time with Roniacol (Table 1). In both patients it was evident that the drug effect persisted for 2 to 7 days following discontinuance of the drug. The most significant measurement appears to be the last one made during the period on drug rather than the mean reading for the entire period. Skin temperatures were recorded on 3 patients near the end of the period on the drug and while on placebo therapy. One showed significantly higher temperatures while on the drug (Table 2). Roniacol® was generally well tolerated although 2 patients initially noted marked flushing of the face and neck. This was even more striking following intravenous administration.

3. Priscoline® was given in dosage of 75 mg., 4 times a day. All patients noted improvement in claudication. The 3 who suffered from night cramps noted complete relief on Priscoline®; the night cramps returned abruptly on discontinuance. Two (RA and VR) had increase in claudication time on the ergometer while the other 2 (MR and JK) showed no change (Table 1). Two had higher skin temperatures on Priscoline® than on the placebos (Table 2).

SKF 688A was given in dosage of 40 mg. every 8 hours. Two patients noted substantial relief of claudication. The other 2 did not. Night cramps were moderately improved in 1, slightly in another but appeared to be worse in a third. Two had increase in claudication time, the other 2 showed no change. The temperatures were higher than on placebos in all 3 patients tested (Table

TABLE 1.—EFFECT OF THREE VASODILATOR DRUGS ON CLAUDICATION TIME

(Claudication time given in seconds)

	Control	*Ron. 600 mg. q.d.*	*Ron. Plac. 600 mg. q.d.*	*688–A 120 mg. q.d.*	*688–A Plac. 120 mg. q.d.*	*Pris. 300 mg. q.d.*	*Pris. Plac 300 mg. q.d.*
R. A.	55	266	78	213	215	362	205
V. R.	218	378	210	238	237	416	413
M. R.	48	80	69	93	107	95	68
J. K.	135	110	130	119	90	91	140

TABLE 2.—EFFECT OF THREE VASODILATOR DRUGS ON SKIN TEMPERATURE OF THE TOES

(Skin temperature given in °C.)

	Ron. 600 mg. q.d.		*Ron. Plac. 600 mg. q.d.*		*688–A 120 mg. q.d.*		*688–A Plac. 120 mg. q.d.*		*Pris. 300 mg. q.d.*		*Pris. Plac. 300 mg. q.d.*	
	Rgt	*Lgt*	*Rgt*	*Lgt*	*Rgt*	*Lgt*	*Rgt*	*Lgt*	*Rgt*	*Lgt*	*Rgt*	*Lgt*
V. R.	33.0	33.75	28.5	30.75	31.25	31.75	24.5	23.0	30.75	31.5	28.0	27.5
M. R.	31.0	30.5	31.0	30.5	26.75	26.75	22.5	25.75	29.25	29.5	19.5	19.5
J. K.	27.0	26.75	29.25	23.5	29.5	31.0	21.5	22.0	21.5	21.0	19.5	23.75

1). One showed significant skin temperature increase on SKF 688A but only equivocal rise on oral Roniacol® and none on oral Priscoline® (Table 2). Three patients showed decreased appetite. All patients had blurred vision and 2 were tested for pupillary responses. The pupils of both patients were contracted to about 3 mm. in diameter and would constrict with light but would not dilate with darkness. It was impossible to produce pupillary dilatation despite the use of large amounts of 2.5 and 10% neosynephrine, 10% paredrine and 10% cocaine. All patients developed nasal congestion and 2 noted marked weakness. Two patients showed decreases in blood pressure of 40 to 60 mm. Hg systolic and 10 to 30 mm. Hg diastolic. Two showed no change in blood pressure.

Intravenous Administration. Two patients were given single injections of 100 mg. of Roniacol® intravenously. Both noted marked flushing of the face and neck, along with subjective improvement in claudication. One had a threefold increase in claudication time which persisted for several days. The other had no increase in claudication time with Roniacol on 2 occasions. This patient was given 3.8 gm. of diethylaminoethanol intravenously within a 5-minute period. There was no increase in claudication time. Earlier studies indicated a rise in skin temperature of the toes in 11 of 20 subjects. One patient (JK) was given 75 mg. of Priscoline® intravenously. He showed a marked abrupt rise in both fingers and a later slow rise in both toes. Severe leg cramps were noted about 30 minutes after administration of the drug.

Discussion. Since measurements of peripheral blood flow employed in this study were indirect, the evaluation of vasodilator drugs was difficult. We have attempted to combine several available methods of measurement. Intermittent claudication and night cramps were found to be fairly reliable indicators of drug action. Prolonged drug action was noted to persist sometimes for several days after the drug was discontinued.

The correlation between the spontaneous occurrence of intermittent claudication and claudication time measured on the ergometer was good in 2 patients and was poor in the other 2. It is of interest that in 2 patients (RA and VR) the claudication time never returned to the control period baseline though it showed increases during drug periods and decreases during placebo periods. It is not clear whether the improvement was due to the exercise necessarily connected with repeated tests or to action of the drugs. Two patients (MR and JK) noted marked subjective improvement in intermittent claudication and night cramps, but had no significant changes in claudication time. The other 2 patients (RA and VR) showed more than twofold increase in claudication time with Roniacol® and Priscoline®, and moderate increase with the Dibenamine analogue. With Procaine amide no changes in claudication times were observed.

Skin temperatures of the toes tended to be higher when the patients were on drug therapy than on the corresponding placebo.

Following a single intravenous injection the blushing effect of Roniacol® is a constant feature, accompanied by significant elevations in temperature of the blushing area. However, with chronic oral use of the drug, the tendency to blush becomes progressively less evident, while there is apparently a greater effect on the toes. These differences in the site of maximum effect and change in effect with daily dose suggest that it might not be reliable to test by a single large dose a vasodilator which is to be used clinically

in prolonged, continuous administration.

The skin temperature responses of RA were erratic, possibly due to hyperhidrosis, and he was excluded from that type of measurement as unsuitable.

Side effects included occasional mild gastric irritation and anorexia with all of the drugs. Flushing of the face and neck was noted with Roniacol® following initial doses.

The action of SKF 688A persisted for approximately a week after the drug was discontinued. Such delaved action might be expected from the fact that Dibenamine® is taken up by the fat depots of the body and then slowly released[4].

Roniacol® seemed to have a greater effect on intermittent claudication, and Priscoline® on night cramps. SKF 688A showed definite vasodilator properties; they were complicated by other adrenergic blocking effects. These included the interesting effect on the pupillary mechanism. Pronestyl® had no measurable vasodilator effect.

Lack of agreement among the different tests used in a given patient suggests that a better evaluation of a vasodilator drug can be had by using multiple tests than by any single test.

Summary. 1. The response of intermittent claudication, night cramps, claudication time and skin temperature was observed with Pronestyl®, Roniacol®, Priscoline® and a new adrenergic blocking agent (SKF 688A) in 4 male patients with arteriosclerosis obliterans.

2. Intermittent claudication and night cramps were improved with Roniacol® and Priscoline®, and to a lesser degree with SKF 688A. No effect was noted with Pronestyl®.

3. The claudication times were significantly lengthened in only 2 of the 4 patients on Roniacol®, Priscoline® and SKF 688A. There was no change with Pronestyl®.

4. The skin temperature of the great toes was elevated on SKF 688A in all of the 3 patients tested; and in 2 of the 3 on Roniacol® and on Priscoline®.

5. No single test seems adequate to describe vasodilator effects.

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THE ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH HYPERCALCEMIA AND HYPOCALCEMIA*

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The changes in the human electrocardiogram with hypercalcemia and hypocalcemia have been described by many investigators[3,7,8,10,11,14,17,18]. The most constant and outstanding change described is alteration of the QT interval. With hypercalcemia the QT interval is shortened, whereas in hypocalcemia it is abnormally prolonged. The shortened QT interval in hyperparathyroidism returns to normal after removal of the parathyroid tumor[11], and the prolonged QT interval in cases of tetany decreases as the serum calcium level rises with treatment[8,17]. The prolonged QT interval in patients with hypocalcemia indicates lengthening of electrical systole, but not of mechanical systole[3]. Wofford and Ernstene[18], using the Chart of White and Mudd, found that the QT interval was prolonged in most of 15 patients with hypocalcemia.

Recently Ernstene and Proudfit[10] have pointed out that in cases of hypocalcemia the prolongation of the QT interval is actually due to lengthening of the ST segment. Marzahn[12] also stressed the importance of the lengthened ST segment in patients with low levels of serum calcium.

It is the purpose of this report (a) to describe and emphasize the electrocardiographic changes in patients with hypercalcemia and hypocalcemia; (b) to correlate the level of serum calcium with the corrected QT interval and the duration of the ST segment in these 2 conditions; and (c) to differentiate these electrocardiographic changes from those associated with other conditions.

Material and Method. Between September, 1949 and December, 1951 2 patients with hypercalcemia and 10 patients with hypocalcemia due to various causes were admitted to the Hospital. In this Hospital the normal range of serum calcium varies between 9 and 11 mg. per 100 cc. (4.5–5.5 mEq./L.). All the patients included in this report had had a serum calcium level either above 13 mg. per 100 cc. (6.5 mEq./L.) or below 7 mg. per 100 cc. (3.5 mEq./L.) on 1 or more occasions.

One or more electrocardiograms were taken on each patient at the same time that blood samples were obtained for the determination of serum electrolyte. In several instances, simultaneous electrocardiograms and serum calcium determinations were followed at regular intervals for a number of days until the discharge or death of the patient.

In about one-half of the patients, the disturbance of calcium metabolism was not clinically suspected until the electrocardiogram was read. In each instance, the blood samples obtained on the same day showed an abnormal serum calcium level and confirmed the electrocardiographic interpretation.

The electrocardiogram usually consisted of 6 limb leads and 6 or 3 precordial leads (V_{1-6}, or V_1, V_3, and V_5). The QT interval was measured in the 3 standard limb leads and in the 3 precordial leads (usually V_4, V_5, and V_6). An average value obtained in these 6 leads was used. The corrected QT interval or QTc was derived by using the modified Bazett's formula, $QTc = \frac{QT}{\sqrt{RR}}$[15]. The upper and lower limits of the normal for the QTc

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interval in this Hospital are 0.43 and 0.36 respectively. The ST segment was usually measured in both leads I and V_5. The upper limits of the duration of the ST segment have been adapted from data published by Ashman and Hull[2].

Results. The pertinent data, including the diagnoses, the electrocardiographic measurements, and the blood chemical analyses for these 12 patients are presented in Table 1.

HYPERCALCEMIA. Two patients had hypercalcemia for varying periods. One patient (E. S.) had a normal QTc interval but the ST segment was shortened. The outstanding electrocardiographic changes of the other patient (R. S.) were shortening of both the ST segment and the QT interval. The case report of the second patient is presented as an illustration.

CASE 1. R. S. (Fig. 1) was a 47-year old white female who was admitted with a tentative diagnosis of anemia. Physical examination showed pallor, slight icterus, marked splenomegaly and minimal enlargement of the liver. Laboratory findings included hemoglobin 8.4 gm., hematocrit 21%, icterus index 27, serum bilirubin 4 mg. per 100 cc., and a strongly positive Coomb's test. The

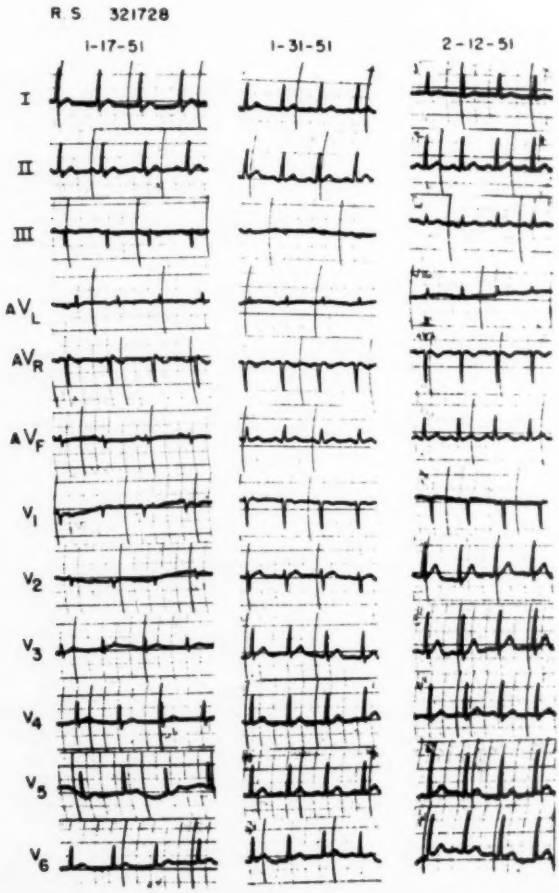

FIG. 1.—Hypercalcemia. Case 1. (R. S.). See text and Table 1 for explanation.

TABLE 1.—DATA FROM CHEMICAL ANALYSIS OF THE BLOOD AND ELECTROCARDIOGRAPHIC MEASUREMENTS IN TWO PATIENTS WITH HYPERCALCEMIA AND TEN PATIENTS WITH HYPOCALCEMIA

					*Chemical Analysis of the Blood**				*Electrocardiographic Data†*				
Case	*Age*	*Sex*	*Diagnosis*	*Date*	*Ca*	*P*	*K*	*A/G*	*H.R.*	*ST*	*QT*	*QTc*	*Remarks*
R. S.	47	F	Acute leukemia (parent cell type)	1/17/51	16.1	3.2	3.9	3.8/2.5	105	0.04	0.24	0.32	
				1/26/51	16.6	4.8	3.3	4.2/2.7	115	0.04	0.26	0.36	
				2/8/51	16.0	5.3	4.5	4.1/2.2	133	0.05	0.25	0.37	
				2/12/51	12.2	...	4.2	3.8/2.3	120	0.06	0.26	0.37	
				2/19/51	10.5	2.3	4.3		150	0.05	0.25	0.40	Died, autopsy
E. S.	35	F	(1) Hyperparathyroidism	9/30/49	13.1	2.6	...	...	103	0.06	0.32	0.42	Heart enlarged. Parathyroid tumor removed on 11/19/49; improved
			(2) Hypertension, essential	10/5/49	13.5	2.8	...	...	105	0.05	0.30	0.40	
				11/30/49	10.6	3.8	...	...	102	0.07	0.33	0.43	
J. P.	45	F	(1) Congenital polycystic kidney	4/27/50	4.0	6.6	...	4.2/2.4	71	0.24	0.44	0.48	Improved
				5/1/50	5.9	...	...	...	70	0.26	0.46	0.50	
			(2) Uremia	3/1/51	8.0	6.5	...	...	87	0.16	0.34	0.41	
			(3) Hypertensive cardiovascular disease	3/9/51	8.0	5.2	...	4.2/1.9	107	0.15	0.34	0.45	
				3/13/51	7.8	7.1	5.1	...	102	0.17	0.37	0.48	
				4/11/51	6.0	...	...	...	90	0.17	0.37	0.45	Improved
M. R.	40	F	Cirrhosis of liver	11/9/50	6.9	...	3.7	3.2/3.5	100	0.22	0.44	0.55	Died, autopsy
L. T.	73	M	(1) Arteriolar nephrosclerosis (2) Uremia	12/12/50	4.7	11.4	...	4.2/2.2	82	0.20	0.45	0.52	Died, autopsy
R. F.	31	F	(1) Thyrotoxicosis	10/27/50	5.2	4.0	...	...	133	0.17	0.34	0.50	
			(2) Acute pericarditis	11/2/50	8.8	3.6	...	...	94	0.14	0.37	0.46	Improved
M. M.	7	M	(1) Subacute glomerulonephritis	1/3/51	7.6	...	5.8	3.5/2.7	67	0.13	0.37	0.39	
				1/17/51	5.6	...	6.3	...	83	0.18	0.38	0.45	
			(2) Subarachnoid hemorrhage	1/26/51	5.8	...	4.2	3.6/3.0	81	0.17	0.40	0.47	
			(3) Acute pericarditis	1/31/51	6.4	...	5.3	2.6/2.2	94	0.17	0.37	0.46	
				3/5/51	6.8	...	7.2	...	94	0.19	0.36	0.44	
				3/17/51	7.6	...	7.0	...	118	0.13	0.30	0.42	Died, autopsy
E. F.	9	F	Hypoparathyroidism	3/6/51	4.4	7.4	...	...	103	0.23	0.38	0.50	
				3/21/51	4.8	7.3	...	...	100	0.22	0.39	0.49	Improved
D. O'B.	19	F	(1) Chronic glomerulonephritis	8/18/51	3.5	15	9.7	3.1/2.3	107	0.20	0.38	0.51	Electrocardiogram on 8/19/51 showed a pattern of posteroseptal myocardial infarction. Died, autopsy. No myocardial infarction
			(2) Potassium intoxication	8/19/51	3.0	14.6	...	...	93	0.20	0.42	0.52	
M. G.	12	M	Hydronephrosis, bilateral	2/14/51	4.8	6.3	5.0	4.3/2.8	97	0.16	0.38	0.48	
				3/5/51	6.8	6.8	...	...	107	0.14	0.33	0.44	Improved
D. B.	40	F	(1) Addison's disease	3/31/50	7.7	3.7	3.4	4.5/1.8	77	0.18	0.42	0.48	
			(2) Hypoparathyroidism, postoperative	4/6/50	6.1	3.3	2.8	...	80	0.20	0.45	0.52	Improved
E. L.	60	M	(1) Osteomalacia	1/21/50	5.9	...	...	...	85	0.21	0.40	0.48	
			(2) Adult rickets	3/11/50	8.5	...	...	...	85	0.15	0.34	0.41	Improved

* Ca—calcium in mg. per 100 cc., P—phosphorus in mg. per 100 cc., K—potassium in mEq./L., A/G—albumin/globulin in gms.%
† H.R.—heart rate/minute, ST—ST segment in seconds, QT—QT interval in seconds, QTc—QT interval corrected for heart rate

working diagnosis was acquired hemolytic anemia, and an attempt was made to prepare her for splenectomy. She was given a course of ACTH. However, her condition deteriorated gradually and she developed hyperpyrexia and tachycardia. Sternal marrow biopsy suggested a reticulum cell sarcoma, but at postmortem examination the final diagnosis was acute leukemia of parent cell type.

The electrocardiogram made on January 17, 1951 showed a very short ST segment (0.04 second) and the QTc interval was 0.32. The diagnosis of hypercalcemia was first suggested by the characteristic electrocardiographic changes. A blood specimen obtained on the same day had an exceedingly high serum calcium level (16.1 mg. per 100 cc). A serum calcium level on February 12, 1951 declined to 12.2 mg. per 100 cc. with treatment; and at the same time the electrocardiogram showed lengthening of both the QTc interval (0.37) and the ST segment. In addition, the amplitude of the T wave in the precordial lead increased as the level of the serum calcium fell. However, there was no deviation of the ST segments, and both the QRS complex and the PR interval were unchanged.

The total serum protein and the albumin-globulin ratio were normal throughout her course. The level of serum potassium varied between 3.3 and 4.5 mEq./L. (Table 1).

HYPOCALCEMIA. Ten patients showed a subnormal serum calcium level for varying periods. The most conspicuous electrocardiographic changes associated with hypocalcemia were prolongation of the ST segment and the QT interval (Figures 2 to 5). When the serum calcium level falls below 7 mg. per 100 cc. (3.5 mEq./L.), the duration of the ST segment usually exceeds the upper limit of the normal values adapted by Ashman and Hull[2]. Prolongation of the ST segment is usually seen most clearly in the left precordial leads (V_4, V_5 and V_6) and in leads I and aV_L. The following case illustrates the electrocardiographic pattern.

CASE 2. J. P., a 45-year old woman was first admitted on April 27, 1950 with a history of shaking for 3 days. She had been known to have congenital polycystic kidneys and hypertensive cardiovascular disease for more than 10 years. The pertinent physical findings on admission were pallor, edema of the ankles, hypertensive retinopathy, a blood pressure of 170/110 mm. Hg and large lobulated masses in the abdomen. The Chvostek and Trousseau signs were negative. The urine showed one plus albumin. Blood chemistry showed a serum calcium level of 4 mg. per 100 cc. (2 mEq./L.), serum inorganic phosphorus 6.6 mg. per 100 cc., blood urea nitrogen 95 mg. per 100 cc. The total serum protein was 6.6 gm. per 100 cc., with an albumin-globulin ratio of 4.2/2.4 (Table 1). An electrocardiogram (Figure 2) made on April 27, 1950 showed prolonged QTc interval and ST segment. These changes were interpreted as highly suggestive of hypocalcemia. The next day the serum potassium was 4.8 mEq./L., and the serum sodium 138 mEq./L. After she was given 6 gm. of calcium the level of calcium was 5.9 mg. per 100 cc. and the electrocardiographic changes were still compatible with hypocalcemia. She was discharged on May 3, 1950 with a serum calcium level of 7.6 per 100 cc. (3.8 mEq./L.).

On February 6, 1951 she was readmitted for study. During the period of hospitalization the serum calcium levels varied between 5.2 and 8 mg. per 100 cc. (2.6–4.0 mEq./L.). Several electrocardiograms were made and in each instance both the QT interval and the ST segment were less markedly prolonged than that had been observed during the previous admission. She was finally discharged in improved condition.

Slight depression of the ST segment and appearance of a distinct U wave occurred in one case (M. R., Figure 3), in whom the serum potassium level was 3.7 mEq./L. In the case of R. F. (Figure 4) the QT interval was prolonged to such a degree that the P wave was obscured by the preceding T wave. The T wave was rather high in more than half of the patients with hypocalcemia, although it was low in 3 cases (R. F., M. R., and D. B.). There was no change in either the PR interval or the QRS complex in any of the cases studied.

The duration of the ST segment and the level of serum calcium are generally inversely related in both hyper-

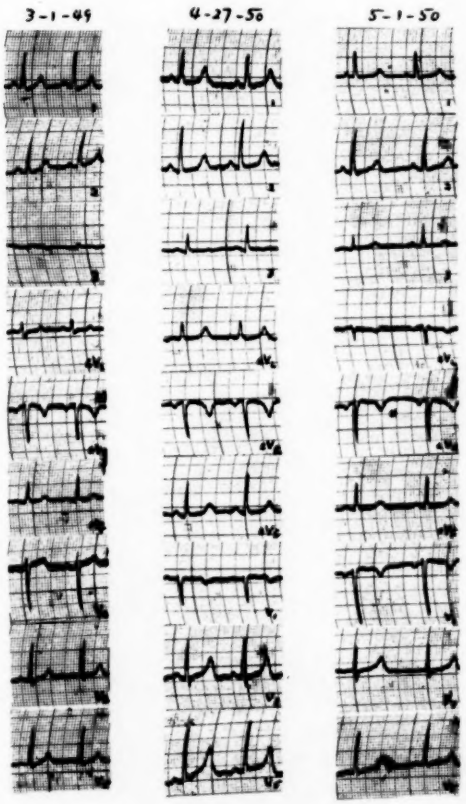

FIG. 2.—Hypocalcemia. Case 2. (J. P.). The electrocardiogram made on March 1, 1949 was essentially normal and the serum calcium level was 9 mg. per 100 cc. (4.5 mEq./L.). The next two tracings showed prolongation of both the ST segment and the QTc interval. The serum calcium level on April 27, 1950 was 4 mg. per 100 cc. (2.0 mEq./L.) and on May 1, 1950, 5.9 mg. per 100 cc. (3.0 mEq./L.). See text and Table 1 for further information.

calcemia and hypocalcemia. A similar inverse relationship exists between the duration of the QTc interval and the serum calcium level. In this series of patients, the coefficient of correlation between the ST segment and the calcium level is −0.84, and that between the QTc interval and the serum calcium level is −0.70. Both figures are considered to be highly significant. Figure 6 shows the graph of the ST segments and the QTc intervals plotted respectively against the serum calcium level in 34 determinations.

Discussion. Our data confirm previous reports that the outstanding electrocardiographic change associated with abnormal serum calcium levels is marked alteration of the QT interval, which in turn is largely due to shortening or lengthening of the ST segment. Both the ST segment and the QTc interval vary inversely with the calcium level. To the writer's knowledge, no correlation between the serum calcium level and the ST segment has been previously reported. In the present series measurement of the ST segment

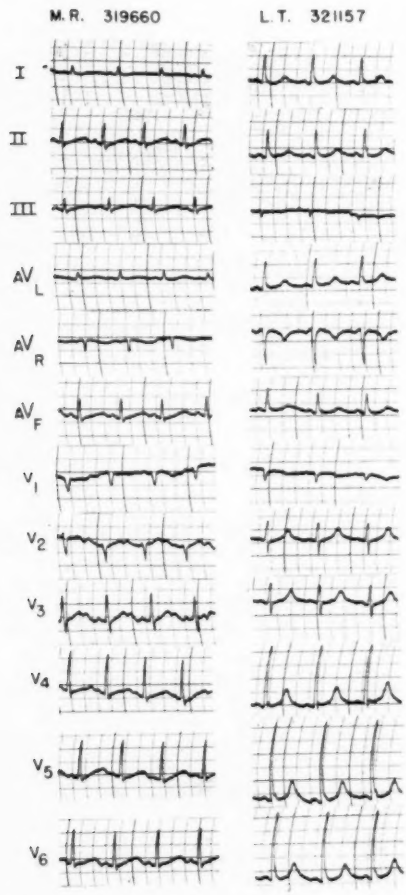

FIG. 3.—Hypocalcemia. Case M. R. The electrocardiogram showed definite ST depression, a distinct U wave in the precordial leads, and prolongation of the ST segment and the QTc interval. The serum calcium level was 6.9 mg. per 100 cc. (3.5 mEq./L.) and the serum potassium was 3.7 mEq./L. The ST depression and appearance of U wave were probably due to concomitant hypopotassemia.

Case L. T. Distinct prolongation of both the ST segment and QTc interval was demonstrable in the electrocardiogram. The serum calcium level was 4.7 mg. per 100 cc. (2.4 mEq./L.).

as illustrated by case E. S. is a more accurate diagnostic aid than the QT interval in detecting hypercalcemia.

Wofford and Ernstene[18] did not find a mathematical relationship between the measured QT interval and the serum calcium level. However, recalculation of their data shows that a highly significant correlation ($N = 47$, $r = -0.65$) exists between the serum calcium level and the *corrected* QT interval. As pointed out by Taran and Szilagyi[15] and others[1] the measured QT interval should be corrected for heart rate in order to evaluate its variation under changing conditions.

The QTc interval is usually short in hypercalcemia, especially when the

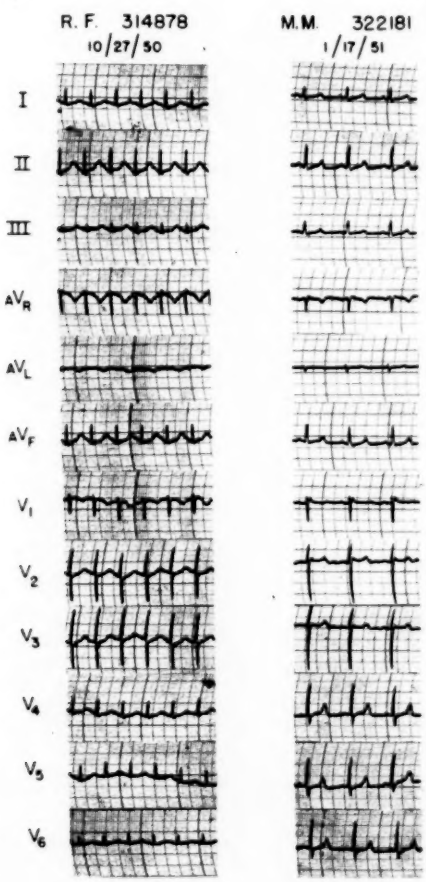

FIG. 4.—Hypocalcemia. Case R. F. The electrocardiogram showed a sinus tachycardia with definite prolongation of the ST segment and the QTc interval. The QT interval was prolonged to such a degree that the P wave was obscured by the preceding T wave. The serum calcium level was 5.2 mg. per 100 cc. (2.6 mEq./L.).

Case M. M. The changes are similar to those seen in the electrocardiogram made on case L. T. The serum calcium level was 5.6 mg. per 100 cc. (2.8 mEq./L.).

serum calcium exceeds 13 mg. per 100 cc. (6.5 mEq./L.). Shortening of the QT interval is principally due to shortening of the ST segment. The ST segment in 1 of our cases (R. S.) was only 0.04 seconds when the serum calcium level reached 16.1 mg. per 100 cc. (8.0 mEq./L.). As the serum calcium became lower, the ST segment began to lengthen in the electrocardiogram.

Marked shortening of the QT interval has been reported to occur in 3 conditions: hypercalcemia[11], digitalis effect[6], and acute pericarditis[16]. With digitalis effect, the shortened QTc interval is invariably accompanied by sagging or depression of the ST segment and a diaphasic T wave. Furthermore, appearance of ventricular premature beats and prolongation of

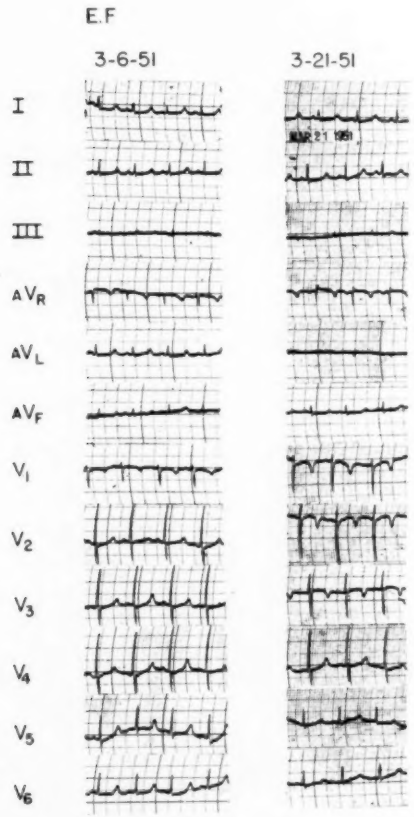

FIG. 5.—Hypocalcemia. Case E. F. The electrocardiogram showed characteristic changes of hypocalcemia—distinct prolongation of the ST segment and the QTc interval. The serum calcium levels on March 6, and March 21, 1951 were, respectively, 4.4 mg. per 100 cc. (2.2 mEq./L.) and 4.8 mg. per 100 cc. (2.4 mEq./L.).

auriculo-ventricular conduction are not uncommon. Distinct electrocardiographic changes other than shortening of the QT interval occur in many cases of acute pericarditis. These include elevation of the ST segment in the precordial leads and the limb leads, except in V_R or aV_R where the ST segment is depressed. Later in the course of pericarditis, the ST segment becomes isoelectric and the T wave may be inverted. Therefore, electrocardiographic differentiation of hypercalcemia, digitalis effect and acute pericarditis is possible in most cases.

The electrocardiographic changes with hypocalcemia are the opposite of those of hypercalcemia. The ST segment and the QT interval are prolonged. These changes are frequently demonstrated when the serum calcium level is less than 7 mg. per 100 cc. (3.5 mEq./L.) and they are always observed when the level is 6 mg. per 100 cc. (3 mEq./L.) or less. This agrees well with the observations reported by Reynolds *et al.*[14].

The mechanism of prolongation of the ST segment in hypocalcemia is still obscure. It has been explained as

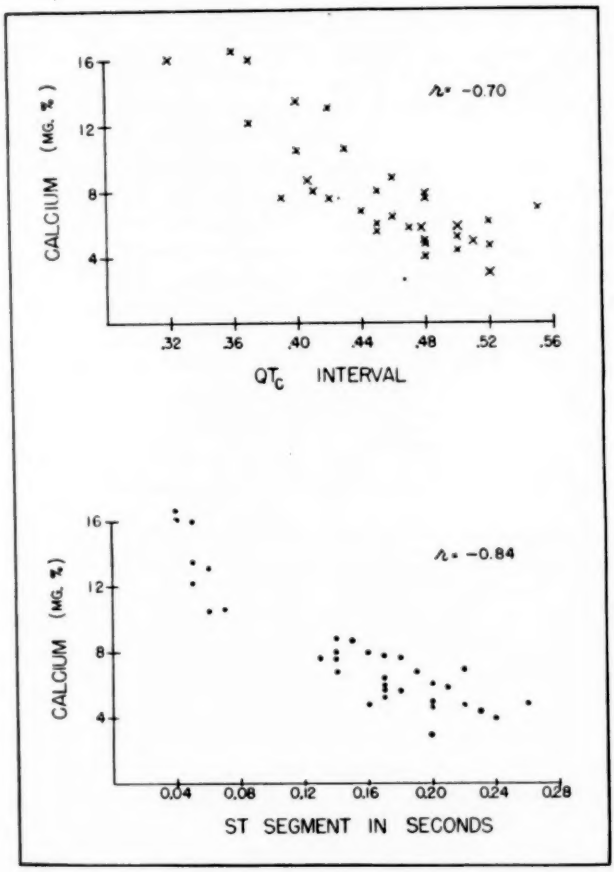

FIG. 6.—This graph shows the correlation between serum calcium level and QTc interval (above) and between serum calcium level and duration of ST segment (below).

a tetanic state of cardiac muscle[12]. It is interesting to note that in 2 of our cases, there was no evidence of tetany, even when the serum calcium level was as low as 5 mg. per 100 cc. (2.5 mEq./L.).

Electrocardiographic patterns in hypopotassemia have been described in detail by Bellet and associates[4,13]. Prolongation of the QT interval is a predominant feature in both hypopotassemia and hypocalcemia. Sometimes it is not possible to distinguish the 2 conditions by the changes in the electrocardiogram alone[4,5]. However, Ernstene and Proudfit[10] pointed out that prolongation of the QT interval with hypocalcemia is largely due to lengthening of the ST segment. On the other hand, in hypopotassemia it is caused principally by widening of the T wave. Wofford and Ernstene[18] state further that an abnormal serum potassium concentration seems more

important than hypocalcemia in prolonging the QT interval. On the other hand, Reynolds *et al.* stated that the magnitude of prolongation of the QT interval is generally greater with hypocalcemia than with hypopotassemia of a like degree[14].

Engel *et al.*[9] reported interesting findings in 2 patients with simultaneous hypopotassemia and hypocalcemia. The electrocardiographic abnormalities were characteristic of hypopotassemia and were abolished by treatment with potassium, but were not affected by calcium administration. However, Bellet and associates[5,13] reported that it is necessary to administer both calcium and potassium in such cases to restore the electrocardiogram to normal configuration.

Electrocardiographic changes in patients with hypopotassemia usually include lowering or inversion of the T wave, depression of the ST segment and the appearance of the U wave, in addition to the prolonged QT interval. These changes have been emphasized by Bellet and associates[4].

In our experience the electrocardiogram in patients with hypocalcemia seldom shows any changes other than prolongation of the ST segment and the QT interval. Distinct ST depression associated with rounded, diphasic, or inverted T waves is a very unusual finding in hypocalcemia and is commonly seen with hypopotassemia. Actually in several cases included in this series, the amplitude of the T wave increased when the serum calcium level was low.

Electrocardiographic changes due to quinidine effect might be confused occasionally with those of hypocalcemia. We have recently encountered the electrocardiograms of 4 such cases, in which both ST segment and QT interval were prolonged with no other significant changes. In each case, the dosage of quinidine was more than 2 gm. in 24 hours and the serum calcium level was within normal limits. In the majority of cases, the differentiation between the quinidine effect and hypocalcemia is not a problem. In cases of the former, there is always a history of quinidine therapy and the prolonged QT interval may be associated with widening of the QRS complex.

Summary. (1) The electrocardiographic changes in 2 cases of hypercalcemia and 10 cases with hypocalcemia are described.

(2) With hypercalcemia the characteristic findings are shortening of the ST segment and the QT interval. With hypocalcemia the ST segment and the QT interval are prolonged. These changes are always seen when the serum calcium level increases to 13 mg. per 100 cc. (6.5 mEq./L.) or decreases to 6 mg. per 100 cc. (3.0 mEq./L.). The changes in the duration of the ST segment and QT interval may serve as an important adjunct in the qualitative diagnosis of hypercalcemia or hypocalcemia in the absence of other electrolyte disturbance.

(3) There is a significant correlation between the serum calcium level and both the ST segment and the corrected QT interval.

(4) The electrocardiographic differentiation between disturbances in serum calcium levels and other conditions producing similar changes is discussed.

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ELECTROCARDIOGRAPHIC CRITERIA OF LEFT VENTRICULAR HYPERTROPHY*

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The changes in the QRS complex associated with left ventricular hypertrophy (referred to as LVH) include: (1) in the standard limb leads, high voltage of R_1 and S_3[2]; (2) in the unipolar limb leads, high voltage of RaVL in horizontal hearts and high voltage of RaVF in vertical hearts[1]; (3) in the precordial leads, high voltage of R in leads from the left precordium, high voltage of S in leads from the right precordium, and prolongation of the time of onset of the intrinsicoid deflection in leads from the left precordium[15,16]. There have been several attempts to define more specifically these electrocardiographic criteria of LVH. Gubner and Ungerleider[2] proposed that LVH is present if the sum of R_1 and S_3 exceeds 25 mm., which was the maximum value they found in 99% of 460 normal individuals with left axis deviation. Sokolow and Lyon[12] in a study of 151 normal individuals found the following maximum amplitudes: R_{V5}, 26 mm.; R_{V6}, 22 mm.; the sum of R_{V5} or R_{V6}, and S_{V1}, 35 mm.; RaVL, 10 mm., and the maximum time of onset of the intrinsicoid deflection in V_5 and V_6, 0.05 seconds. Observing that these

TABLE 1.—ELECTROCARDIOGRAPHIC (QRS) CRITERIA OF LVH

Description	*Symbol*
1. Sum of amplitude of R_1 and S_3 equals 25 mm. or more	$R_1 + S_3 = 25$ or $>$
2. Amplitude of RaVL exceeds 11 mm.	RaVL > 11
3. Amplitude of R_{V5} exceeds 26 mm.	$R_{V5} > 26$
4. Amplitude of R_{V6} exceeds 26 mm.	$R_{V6} > 26$
5. Time of onset of intrinsicoid deflection in V_5 or V_6 exceeds 0.05 sec.	ID $V_{5\text{-}6} > 0.05$
6. Sum of amplitudes of R_{V5} or R_{V6} and S_{V1} exceeds 35 mm.	$R_{V5\text{-}6} + S_{V1} > 35$

* Based in part on portion of thesis submitted by Dr. Heine to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, toward the requirements for the degree of Master of Medical Science (M. Sc. (Med.)) for graduate work in Internal Medicine.

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values were frequently exceeded in a group of 147 patients "whose electrocardiograms were abnormal and in whom a cardiac disorder capable of producing increased strain on the left ventricle . . . was present," Sokolow and Lyon[12] listed for the QRS complex the criteria of LVH shown in Table 1.

Our purpose in this study was to evaluate the sensitivity and specificity of these criteria of LVH proposed by Sokolow and Lyon. In a consecutive series of cases, we assayed the electrocardiographic criteria against the diagnosis of LVH as made by non-electrocardiographic standards, that is, teleoroentgenographic evidence of LVH in the presence of an etiological factor for LVH. We also studied the influence on the criteria of the electrical position of the heart and the age of the patient. Abnormalities of ST-T are associated frequently with LVH[3,8] and are included by Sokolow and Lyon[12] as criteria of LVH. Since such abnormalities of ST-T occur under many other circumstances, however, we did not consider them as primary criteria of LVH in this study.

Material and Method of Study. The cardiac evaluations of 1064 consecutive male veterans were reviewed. The studies included the clinical examination and a technically satisfactory teleoroentgenogram and electrocardiogram. In each case the presence of any of the electrocardiographic criteria of LVH (Table 1) was noted, and the Roentgen-clinical classification with regard to LVH was determined.

ROENTGEN-CLINICAL CLASSIFICATION. The clinical examinations were reviewed and the following considered as etiological factors for LVH: hypertension (blood pressure in excess of 150/90), aortic insufficiency, aortic stenosis and mitral insufficiency. Teleoroentgenograms had been taken at the end of normal inspiration at a target-film distance of 6 feet, in the postero-anterior and in the right and left anterior oblique positions with barium outlining the esophagus. The heart was considered enlarged when the transverse diameter was greater than 10% above the normal value for height and weight as expressed in Ungerleider-Clark prediction tables[13]. Except where the right ventricle or left atrium appeared to be definitely enlarged, the increase in transverse diameter was attributed to the left ventricle. In no instance was a diagnosis of hypertrophy of the left ventricle made solely on the basis of contour (increased convexity or lengthening of the left border), in the absence of an abnormally large transverse diameter. From the roentgenographic and clinical findings, the following Roentgen-clinical classification was then made: (1) LVH: both (a) roentgenographic evidence of LVH and (b) an etiological factor for LVH; (2) possible LVH: either (a) or (b); (3) no LVH: neither (a) nor (b).

ELECTROCARDIOGRAMS had been taken in the supine position with the Cambridge Simpli-trol Electrocardiograph Machine, 12 leads being routine: 1, 2, 3, aVR, aVL, aVF, V_1, V_2, V_3, V_4, V_5, V_6. The instrument is so constructed that for the aV and V leads a 5000 ohm resistance was interposed in the wire from each extremity to the central terminal. The standardization, recorded in all leads, was checked (1 cm. = 1.0 mv.) and where necessary, the proper calibration correction was made. All electrocardiograms were analyzed for the presence of any of the QRS criteria of LVH enumerated by Sokolow and Lyon[12] (Table 1). The amplitudes of the R and S waves were measured from the top and bottom of the baseline, respectively, to the highest or lowest point of the deflection. The average measurement of 3 complexes was recorded. The time of onset of the intrinsicoid deflection was measured from the onset of the QRS to the peak of the R wave. In addition, notation was made of ST-T abnormalities (ST segment depression and/or flattening to inversion of T waves). For each electrocardiogram, the electrical position of the heart[15] was recorded. There were deleted from further consideration all cases in which the electrocardiographic configuration might disturb the patterns upon which the criteria of LVH are based: namely, myocardial infarction, bundle branch block, intraventricular conduction defect (QRS duration 0.11 seconds or more), complete auriculo-ventricular block, right ventricular hypertrophy, and aberrant auriculo-ventricular conduction (Wolff-Parkinson-White Syndrome).

Of the original 1064 cases, 139 were excluded because the electrocardiographic or roentgenographic configurations interfered with the diagnosis of LVH. There remained for detailed analysis 925 cases, which pre-

sented the following Roentgen-clinical diagnoses: LVH, 149 cases; possible LVH, 505 cases; no LVH, 271 cases. Of those with possible LVH, 492 cases were so classified because they had only an etiological factor for LVH. The remaining 13 cases had an abnormal transverse diameter but no etiological factor. Of the 271 cases with no LVH, 248 had no evidence of heart disease and 23 were instances of isolated mitral stenosis.

Results. The incidence of each electrocardiographic criterion of LVH and its correlation with the Roentgen-clinical diagnosis of LVH are shown in Table 2.

SENSITIVITY OF CRITERIA. The incidence of each electrocardiographic criterion of LVH with reference to the 149 cases of LVH (Roentgen-clinical diagnosis) was considered a measure of the sensitivity of that criterion. As noted in Table 2, the highest sensitivity was exhibited by $R_{V5,6}+S_{V1}>35$ which was positive in 106 (71%) of the 149 cases with a Roentgen-clinical diagnosis of LVH. ID $V_{5,6}>0.05$ displayed the lowest sensitivity (11%). Of the 180 cases in which any 1 or more of the criteria were posititive, $R_{V5,6}+S_{V1}>35$ was positive in 170 instances, which is further indication of the sensitivity of this criterion.

SPECIFICITY OF CRITERIA. The incidence of each electrocardiographic criterion with reference to the 271 cases of no LVH was considered a measure of the lack of specificity of that criterion. All criteria displayed a high degree of specificity. Only $R_{V5,6}+S_{V1}>35$ was associated in any instance with a Roentgen-clinical diagnosis of no LVH and this in only 4 (1.5%) of 271 cases. Thus, the criterion with the highest sensitivity was the only one that showed less than complete specificity. In none of these 4 cases were there any other electrocardiographic abnormalities, nor was there any clinical or roentgenographic evidence of heart disease.

ELECTRICAL POSITION. The criteria $R_1+S_3=25$ or $>$ and RaVL >11 (which were usually positive in the same patients) appeared only in association with hearts in the horizontal or semi-horizontal position. This distribution is not unexpected, inasmuch as the horizontal position tends to make for a tall R in aVL and for a deep S in 3. If only the 60 cases of LVH with horizontal or semi-horizontal heart positions are considered, the sensitivity of both $R_1+S_3=25$ or $>$ and RaVL >11 was 45%. The criteria $R_{V5}>26$ and $R_{V6}>26$ were positive in a higher proportion of cases with hearts in the semi-vertical and vertical positions than the other positions. $R_{V5,6}+S_{V1}>35$

TABLE 2.—INCIDENCE OF ELECTROCARDIOGRAPHIC CRITERIA OF LVH AND CORRELATION WITH ROENTGEN-CLINICAL DIAGNOSIS IN 925 CASES

		Roentgen-clinical Diagnosis					
		LVH (149 Cases)		*Possible LVH (505 Cases)*		*No LVH (271 Cases)*	
Criterion	*Number Cases with Criterion Positive*	*Number*	*Percent**	*Number*	*Percent**	*Number*	*Percent**
$R_1+S_3=25$ or $>$	34	28	19	6	1.2	0	0
$R_{aVL}>11$	34	28	19	6	1.2	0	0
$R_{V5}>26$	78	58	39	20	4.0	0	0
$R_{V6}>26$	39	37	25	2	0.4	0	0
ID $V_{5,6}>0.05$	21	17	11	4	0.8	0	0
$R_{V5,6}+S_{V1}>35$	170	106	71	60	12	4	1.5

* Percent of cases with respective Roentgen-clinical diagnosis.

occurred in a high percentage of cases with all heart positions.

Limb lead criteria for hearts whose electrical positions tend toward the vertical were not proposed by Sokolow and Lyon[12]. Goldberger[1] had indicated that 20 mm. should be considered the maximum normal amplitude of the R wave in aVF, and that if this figure is exceeded LVH is present. Sokolow and Friedlander[11] also found 20 mm. to be the maximum normal value for RaVF. The amplitude of RaVF in our 149 cases with a Roentgen-clinical diagnosis of LVH exceeded 20 mm. in only 2 cases. This represented 1.3% of the entire group of 149 cases with LVH, and 6% of the 36 cases with LVH in which the electrical position was vertical or semi-vertical. In both of these cases the criterion $R_{V5} > 26$ was also positive.

Age. The criteria $R_1 + S_3 = 25$ or $>$ and RaVL >11 occurred primarily in the patients over age 40. On the other hand, the criteria $R_{V5} > 26$ and $R_{V6} > 26$ showed their highest incidence in the group under age 40. $R_{V5,6} + S_{V1} > 35$ occurred in a high percentage of cases of all ages.

It is of interest that in the 149 patients with a Roentgen-clinical diagnosis of LVH the heart positions tended toward the vertical in the younger patients and toward the horizontal in the older patients, a trend which is well recognized in normals. Semi-horizontal and horizontal heart positions occurred infrequently in those under age 40 (in only 5, or 11% of 47 cases in this age group).

ST-T Abnormalities. Of the 144 patients with a Roentgen-clinical diagnosis of LVH who were not taking digitalis, 54 had one or more of the QRS criteria of LVH along with ST-T abnormality, 57 had only QRS criteria positive, and 6 had only ST-T abnormality. The remaining 27 had normal electrocardiograms. The high incidence of cases with positive QRS criteria but without ST-T abnormality is noteworthy.

Discussion. Some of the differences in the incidence of the electrocardiographic criteria of LVH in this study and in that of Sokolow and Lyon[12] (Table 3) may be related to the manner in which the cases were selected. Sokolow and Lyon described the features of the electrocardiograms of a group of patients "whose electrocardiograms were abnormal and in whom a cardiac disorder capable of producing increased strain on the left ventricle . . . was present". From a comparison of these features with the normal they derived their criteria of LVH. We, on the other hand, in a series of consecutive cases, have evaluated their proposed electrocardiographic criteria against a non-electrocardiographic criterion against a non-electrocardiographic (Roentgen-clinical) diagnosis of LVH. Recognizing that an increase in the transverse diameter on the teleoroentgenogram does not always indicate the presence of LVH, we have excluded cases in which chambers other than the left ventricle could account for the enlargement, and have required the presence of an etiological factor for LVH to establish the Roentgen-clinical diagnosis of LVH. Since LVH may be present without an increase in the transverse diameter above the normal range, we have considered as possible LVH all cases in which an etiological factor for LVH was present. Contour alone was considered too subjective a basis for making the diagnosis of LVH.

The greater incidence of high voltage in the precordial leads in our series may be related to the fact that the original basis for selection of cases by Sokolow and Lyon did not include high voltage[10]. The relatively low in-

cidence of delayed onset of the intrinsicoid deflection in our study may have two explanations: (a) the possible lower incidence in our material of cases with advanced LVH; (b) our exclusion of cases with electrocardiograms whose total QRS duration was 0.11 sec. or more, as possibly indicating an intraventricular conduction defect. The upper limit of QRS duration considered by Sokolow and Lyon[10] to indicate LVH and not intraventricular conduction defect was "0.12 seconds in the absence of slurring of the QRS complex and a ventricular activation time of less than 0.08 seconds in the left precordial leads." Furthermore, the presence of ST-T abnormalities played no part in the selection of our cases, although it did in those of Sokolow and Lyon.

TABLE 3.—COMPARISON OF INCIDENCE OF ELECTROCARDIOGRAPHIC CRITERIA OF LVH IN THIS STUDY AND IN THAT OF SOKOLOW AND LYON

	This Study (149 Cases)		*Sokolow and Lyon (147 Cases)*	
Criterion	*Number*	*Percent*	*Number*	*Percent*
$R_1 + S_3 = 25$ or $>$	28	19	26	18
RaVL $>$ 11	28	19	33	22
$R_{V5} > 26$	58	39	29	20
$R_{V6} > 26$	37	25		
ID $V_{5\text{-}6} > 0.05$	17	11	52	35
$R_{V5\text{-}6} + S_{V1} > 35$	106	71	48	33
ST–T Abnormal	60	42*	136	93

* Percent of 144 cases (omitting 5 cases who had been taking digitalis).

The only other observations which we have found of the diagnostic value of high amplitude of R in the left precordial leads, are those presented in abstract form by Noth, Myers and Klein[7]. These workers[6] found the average amplitude of R_{V6} to be 16.2 mm. in 84 pathologically proved cases of LVH without associated myocardial infarction or appreciable gross fibrosis, 9.2 mm. in a control series of 52 cases in which the hearts were normal at autopsy, and 10.5 mm. in 50 young male adults with normal hearts by physical and Roentgen examination. For R_{V5}, they found the average amplitude was 17.0 mm. in 58 autopsy proved cases of LVH, 10.7 mm. in 25 autopsy proved normal hearts and 14.1 mm. in the 50 normal male adults. They expressed the opinion that "differentiation between pattern of LVH and of normals could not be made from the amplitude of R waves in V_5 and V_6 alone since the average values were only slightly higher in the former." It is our impression from examination of this detailed data, that there may well be significance in their greater values for the average amplitude of R_{V5} and R_{V6} in the hearts with left ventricular hypertrophy, particularly when compared with the autopsy proved normal hearts.

Certain considerations suggest that one should be cautious of the too rigid application of the QRS criteria under discussion. First, there may be exceptions to the maximum normal values stated by Sokolow and Lyon. Thus, Gubner and Ungerleider[2] did find that in 1% of normals, $R_1 + S_3$ was in excess of 24 mm. Schack, Rosenman and Katz[9] gave a maximum normal value for RaVL of 12 mm. Kossman and Johnston[5,4] have reported amplitudes of R_{V5} up to 33.0 mm. in normals and Va-

quero *et al.*[14] up to 28.4 mm. Also, in our data, $R_{V5,6} + S_{V1}$ exceeded 35 mm. in 1.5% of the normals.

Second, age influences the maximum normal voltage of R_{V5} and R_{V6} as noted by Vaquero *et al.*[14] (whose series of 500 normals is the largest available in the literature). The maximum amplitude of R_{V5} for adults under age 40 was 28.4 mm., in the decade 40 to 50 it was 20.7 mm., from 50 to 60, 17.0 mm. Likewise, the maximum amplitude for R_{V6} for adults under 40 was 24.4 mm., in the decade 40 to 50 it was 19.0 mm., and from 50 to 60, 15.5 mm. This decreasing maximum normal amplitude of R_{V5} and R_{V6} with increasing age suggests that the criteria related to high voltage in the precordial leads should be interpreted more conservatively in younger individuals and more liberally in older ones. The above data also may furnish the explanation for the higher incidence of $R_{V5} > 26$ and $R_{V6} > 26$ in the younger age group in our results, since the higher normal amplitudes in these individuals would allow the value of 26 mm. to be more readily exceeded. The normal amplitudes in children are much higher than in adults and the criteria under discussion cannot be applied to children.

Third, QRS voltage depends not only on age but on the electrical conductivity of the tissues and the distance of the electrode from the heart. Thus emphysema and obesity will result in diminished voltage. On the other hand, a thin chest wall results in high voltage. The criteria for voltage should be interpeted more liberally in the presence of emphysema and a thick chest wall and more conservatively if the subject has a thin chest wall.

Fourth, proper technique of recording the electrocardiogram is essential with regard to standardization, damping and electrode placement. Thus, if for V_5 and V_6 the precordial electrode is placed too far medially, the amplitude of R will often be unduly high, and if too far laterally the amplitude of R will usually be too low.

Fifth, the results in this study were obtained with a string galvanometer with photographic recording. Many of the direct writing electrocardiographs do not yield deflections which are proportionate to the voltage, especially with large deflections. Also, the curvilinear motion of the stylus in many such machines makes difficult accurate measurement of the time of onset of the intrinsicoid deflection.

With the exception of $R_{V6} > 26$, all the criteria for voltage are set 1 mm. above the maximum normal value. For R_{V6}, however the maximum normal value found by Sokolow and Lyon[12] was 22 mm. so that the criterion $R_{V6} > 26$ should be quite rigid. That this is so is suggested by the fact that of our 39 patients with $R_{V6} > 26$, 37 had actual roentgenographic evidence of cardiac enlargement.

Since it is recognized that ST-T abnormalities of the type frequently associated with LVH also occur in other conditions, we did not deem it advisable to analyze them as specific criteria of LVH. We do feel, however, that ST-T abnormalities help in the interpretation of the electrocardiogram in cases where the QRS voltage or time of onset of the intrinsicoid deflection is borderline. Here the differentiation that has to be made is between a normal pattern and one that is diagnostic of LVH. The added presence of ST-T abnormalities makes it more likely that the tracing is abnormal, and, therefore, that the borderline QRS measurements are indicative of LVH. The data previously presented, however, point out that LVH is frequently present with QRS changes alone, in the absence of ST-T abnormality.

The results of our present study do not furnish a basis for conclusions regarding the relative sensitivities of the electrocardiographic and roentgenographic diagnosis of LVH, inasmuch as the latter was used as a standard for evaluating the former.

Summary and Conclusions. 1. The electrocardiographic (QRS) criteria of LVH proposed by Sokolow and Lyon have been evaluated in terms of the Roentgen-clinical diagnosis of LVH (teleoroentgenographic evidence of LVH in the presence of an etiological factor for LVH).

2. The criteria $R_1+S_3=25$ or $>$ and RaVL >11 (which were usually positive in the same patients) occurred only when the heart position was horizontal or semi-horizontal, and much more frequently in patients over than under age 40.

3. The criteria based on high amplitude in the precordial leads were more sensitive than those based on high amplitude in the limb leads. $R_{V5}>26$ and $R_{V6}>26$ showed their highest association with vertical hearts and patients aged under 40. In evaluating high amplitude in the precordial leads, one must consider the normal decrease in amplitude with increasing age, the effect of body build, and the correctness of technique. $R_{V6}>26$ is a more rigid criterion than $R_{V5}>26$ since normally R_{V6} is smaller than R_{V5}.

4. $R_{V5,6}+S_{V1}>35$ was the most sensitive criterion being positive in 71% of the 149 cases with a Roentgen-clinical diagnosis of LVH. Only infrequently was this criterion negative when any of the other criteria were positive. $R_{V5,6}+S_{V1}>35$ is not as specific as the other criteria, however, being positive in 1.5% of the 261 cases with no LVH.

5. ID (time of onset of intrinsicoid deflection) $V_{5,6}>0.05$ displayed the lowest sensitivity. This may be related to the possible exclusion from this study of many cases with advanced LVH.

6. Differences in the incidence of the criteria in our series and in that of Sokolow and Lyon may be related to the differences in the manner of case selection.

7. The occasional finding by others and ourselves of certain of the criteria in normal individuals should lead one to be cautious of their too rigid application.

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THE CLINICAL EFFECTIVENESS OF CERTAIN OF THE HYDROGENATED ALKALOIDS OF ERGOT IN PERIPHERAL VASCULAR DISORDERS*

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The work of Rothlin[10,11] and his collaborators has shown, in animal experiments, that dihydroergocornine, dihydroergocristine and dihydroergokryptine, which when combined in equal parts constitute Hydergine (CCK-179), are all effective in the production of peripheral vasodilatation. Barcroft *et al.*[1] have demonstrated peripheral dilatation in man without decrease in blood pressure in normotensive individuals but with marked depression of blood pressure in subjects with hypertension. Goetz and Katz[5], Kappert[6] and others have demonstrated a wide margin of safety for these drugs in human subjects, and have shown that they are better tolerated and less toxic than their natural non-hydrogenated counterparts. In addition to their peripheral sympathicolytic action and resultant vasodilatation, the hydrogenated alkaloids which comprise Hydergine appear to have a central action, through the vasomotor center[5,6] which is also manifested by a decrease in vascular tone. In the present study the vasodilating action of Hydergine (CCK-179) has been investigated in a series of patients with peripheral vascular diseases.

Methods. The Hydergine (CCK-179) used in this study was in the form of 1-mg. tablets; each tablet contained equal parts of the 3 hydrogenated ergot alkaloids mentioned above. The dosage used varied from 0.5 mg. to 2 mg., administered orally 3 to 4 times per day. There is presented herein an evaluation of the results of treatment with oral Hydergine of 72 cases of various peripheral vascular diseases. The basis of evaluation was primarily clinical in most, and was based upon the effects of the drug on subjective peripheral temperature, intermittent claudication, ulcerative lesions, discomfort, pain and the general well-being of the patient. All patients, except those with acute thrombophlebitis, have been followed for at least 6 months, and some for as long as 22 months.

The total clinical response to the drug in each particular case was designated as "marked" when essentially complete relief of symptoms and complete healing of ulcers were noted, as "moderate" when the most disturbing symptoms were significantly reduced, as "slight" when some degree of improvement was noted but the improvement was less than in the 2 categories listed above, and as "none" when the patient's condition remained essentially unchanged.

Results. The results of oral treatment with Hydergine (CCK-179) in arteriosclerotic peripheral vascular disease, thromboangiitis obliterans or Buerger's Disease, Raynaud's syndrome, acute

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thrombophlebitis and chronic venous insufficiency are summarized in Table 1.

ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE. Thirty-five patients (26 male and 9 female) with arteriosclerotic peripheral vascular disease have been studied (Table 1). Twelve patients had intermittent claudication, only 4 of whom showed improvement. Eight had diabetes mellitus and it was of interest to note that Hydergine did not disturb the control of their diabetes.

There were 6 patients who had ulcerative lesions. All these lesions healed. The ulcers of 4 patients healed within 6 weeks (examples: Case 1, Fig. 1), another healed within 8 weeks; and one ulcer (Case 2, Fig. 2) which was 5 by 5 cm. in area, and had been gradually increasing in size for 9 months at the time treatment was begun, required 6 months for complete healing. The patients with ulcerative lesions were treated as ambulatory cases, and usually granulation at the margins of the lesion began within 1 to 3 weeks after treatment was started.

THROMBOANGIITIS OBLITERANS. Six cases of thromboangiitis obliterans, or Buerger's disease, all in males, have been studied (Table 1). All of these patients showed improvement. One of the patients had been hospitalized for determination of demarcation lines preparatory to amputation of his toes when treatment with Hydergine was started; he improved rapidly and within 2 months he was back at work without the loss of any tissue. Two patients had intermittent claudication which was much improved; a sympathectomy had been done on one of them in 1947. One patient who had a sympathectomy one and one-half years before institution of Hydergine therapy had an ulcer which healed under treatment with the agent. This patient is now at work, and the ulcer remains healed 18 months after treatment was started.

RAYNAUD'S SYNDROME. Eight cases of Raynaud's syndrome, all females, have been treated (Table 1). Only 3 patients showed improvement. The apparent ineffectiveness of Hydergine (CCK-179) in a specifically vasospastic disease is similar to that reported for other methods of treatment.

TABLE 1.—RESULTS OF ORAL TREATMENT WITH HYDERGINE (CCK-179) IN 72 PATIENTS WITH PERIPHERAL VASCULAR DISORDERS

Diagnosis	*No. Cases*	*Ave. Age*	*Age Range*	*Improvement*				
				None	*Slight*	*Moderate*	*Marked*	*Total Improved*
Arteriosclerosis	35	65	46–83	8 (23%)	4 (11%)	14 (40%)	9 (26%)	27 (77%)
Buerger's Disease	6	41	19–56		1 (17%)	3 (50%)	2 (33%)	6 (100%)
Raynaud's Syndrome	8	37	26–53	5 (63%)		2 (25%)	1 (11%)	3 (36%)
Acute Thrombophlebitis	13	39	14–70	4 (31%)	2 (15%)	3 (22%)	4 (31%)	9 (69%)
Chronic Venous Insufficiency	10	57	30–68		1 (10%)	6 (60%)	3 (30%)	10 (100%)

ACUTE THROMBOPHLEBITIS. Thirteen patients, 8 females and 5 males, were treated (Table 1) for short intervals of time during episodes of acute thrombophlebitis. A total of 9 patients showed some improvement during the course of treatment with Hydergine (CCK-179). It was difficult to determine whether the improvement was due to the Hydergine or not, although 5 of these patients had such a degree and such rapidity of improvement in their pain and swelling that at least some benefit may have followed the use of the drug.

CHRONIC VENOUS INSUFFICIENCY. There were 10 patients treated, 3 males and 7 females (Table 1). All showed improvement of at least some degree. The healing of the chronic ulcers

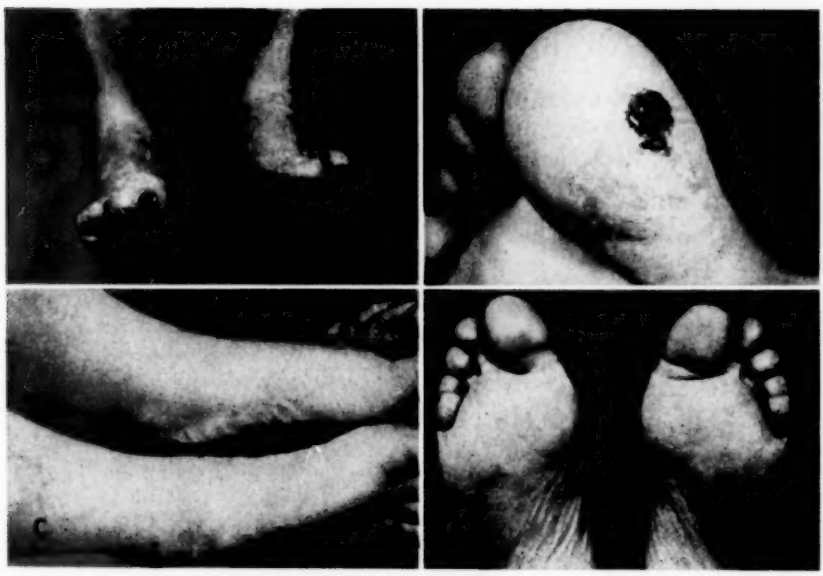

FIG. 1 (Case 1) A) Stasis type of dermatitis of the left foot; B) Dermatitis and ulcer of the great toe, both on right foot; C) Ulcer and dermatitis after 3 weeks on Hydergine therapy; D) After 18 months of continuous treatment with Hydergine (1 mg. t.i.d., a.c.).

(Example: Case 3, Fig. 3) of 5 patients in 6 weeks is the best objective evidence of beneficial action of Hydergine (CCK-179). Improvement in the amount of edema seemed to be definitely related to the use of the drug, since in several of the patients no other treatment, such as elastic supports, or elevation, was instituted and if in use was not altered.

Discussion. A considerable volume of published literature has indicated that the hydrogenated derivatives of ergocristine, ergocornine and ergokryptine individually, or in combination (Hydergine) tend to promote peripheral vasodilatation[1,5,10,11]. Furthermore, and in contrast to some other sympathetic-blocking agents, the evidence indicates that Hydergine has 3 modes of attack: a) diminishing of vasomotor tone[3,4,7] b) peripheral adreno-sympathicolytic activity[3,7] and c) direct (primary and manifest) dilator activity on the smooth muscles of vessel walls [11,12]. On the basis of these vasodilating effects, demonstrated in other studies, the present investigation was instituted in an attempt to evaluate the clinical or practical usefulness of Hydergine in peripheral vascular disease.

The clinical evaluation of any medication is difficult, particularly in a chronic disease in which there are many variables that cannot be controlled, as in peripheral vascular diseases. The results in this investigation were evaluated primarily by subjective and objective observations. Oscillometric and skin temperature measurements would have been helpful, but since many patients show excellent subjective improvement without alteration in the direct measurements, these determinations were not considered to be of great value[9]. Though more objective measurements have been made by most investigators in evaluating various therapeutic measures in peripheral vascular diseases, they have usually been made only in regards to the immediate effect of the measure upon the peripheral circulation. Prolonged continuous observations regarding the effectiveness of a therapeutic measure have necessarily usually been limited to subjective changes noted by the patient and objective observations of the investigator.

Because of the importance of objective evidence, particular significance is attached to the healing of the ulcerations of vascular origin which had been present for several months in 12 patients. The management of these patients was not, in general, altered except by the addition of Hydergine and, where the ulcer was large, the use of vaseline-gauze dressing. The ulcers of all but 4 of these patients were healed within 2 months. While it is admitted that all ulcerative lesions due to peripheral vascular disease may not granulate and heal with oral Hydergine therapy, the success in the 12 cases studied seems to offer strong evidence that the drug promotes vascularity in ischemic areas of the skin.

The percentage of improvement in the arteriosclerotic group constitutes a high proportion of favorable results considering the serious nature of the pathology. Our findings of 66% marked or moderate improvement and 11% slight improvement agree closely with the reports by Popkin[8,9] that his arteriosclerotic patients treated with oral CCK-179 (Hydergine) showed improvement in 72% of the cases. The results of Kappert and Hadorn[7] in 25 arteriosclerotic and 3 diabetic patients seem to be essentially the same as ours, namely, 82% "good" and "fair" responses. Hydergine was used in 16 of these cases, and one or another of the individual alkaloids in the remaining 12. It is also of interest to note that our results appear to be comparable to

those produced by sympathectomy; De Bakey, Creech and Woodhall[2] have recently stated, "The best results (with sympathectomy) were obtained in patients with the least severe disease, over 85% showing definite improvement."

All of the patients with Buerger's Disease or thromboangiitis obliterans showed improvement. Since there were only 6 patients, this rate of improvement is not statistically significant, but could be expected because of the high percentage of improvement in this disease reported by others[7,8,9]. The one patient with a chronic ulcerative lesion present for 1 year had rapid healing, and this seemed to be good objective evidence of the beneficial action of Hydergine.

The relatively poor results in the patients with Raynaud's Syndrome is similar to the reports of Popkin[8,9] and is perhaps to be expected on the basis of generally poor response to all forms of treatment. The prominence of emotional factors in Raynaud's syndrome increases the difficulty of evaluating any therapy.

There can be no conclusions drawn from the treatment of acute thrombophlebitis, but in the treatment of chronic venous insufficiency there was evidence of improvement effected by Hydergine (CCK-179). The 5 patients with ulcerative lesions showed healing quite rapidly after beginning the drug. Since these were chronic ulcers and treatment was not altered in any way, it would appear that this healing was at least in part a response to the vasodilating effect of Hydergine. Most of the patients believed that there was reduction in the amount of edema, a finding reported by others.

The side effects or toxicity to Hydergine (CCK-179), have been minimal. Only one case had clear-cut toxicity. This consisted of nausea and some vomiting when the dosage was increased from ½ mg., 3 times a day, to 1 mg. 3 times per day. This patient, however, had symptomatic relief on ½ mg., 3 times per day. One patient who had had episodes of dizziness and some vertigo noted that this was aggravated by 1 mg. three or four times per day. He received little benefit from ½ mg. 3 times per day. One highly emotional woman complained of mild dizziness on 1 mg. three times per day. All the remaining patients in this report noted no side effects even after specific questioning.

Case Reports. CASE 1. (Arteriosclerotic Ulcer). T.S., a white male, age 74, had a history of diabetes mellitus for 12 years, severe enough to require over 100 units of insulin per day. He had also experienced a myocardial infarction 9 years previous to admission. Recently he had developed a stasis type of dermatitis of both his feet, and an ulcer on the internal aspect of the right great toe, as illustrated in Fig. 1, A. He stated that the ulcer originally developed from a small vesicle. Elevation of the feet produced moderate pallor, and placing them in a dependent position resulted in cyanotic rubor. Pulsations were present but were reduced in posterior tibials and left dorsalis pedis, absent in right dorsalis pedis. No improvement of his lesions (dermatitis or ulcer) resulted from one month of confinement in the hospital with careful regulation of his diabetes. It should be noted that the picture produced in Fig. 1, A, was taken at the end of this initial "control" period.

Treatment consisted of ½ mg. of Hydergine t.i.d., a.c., for 8 days followed by 1 mg. t.i.d., a.c., as continuous (permanent) therapy. The improvement after 3 weeks of treatment with Hydergine is indicated in Fig. 1, B and C. At the end of 6 weeks the ulcer had completely healed. During the succeeding 8 months of treatment the feet have remained in good condition as is shown in Fig. 1, D, taken at the end of this time.

CASE 2. (Arteriosclerotic Ulcer). J. R., a white male, age 67, had complained for several years of intolerance to cold which necessitated the wearing of wool socks in cold weather. A small lesion was present above the left lateral malleolus, which had continued to enlarge over a period of 9 months. Posterior tibial pulsations could not be pal-

FIG. 2 (Case 2) A) Arteriosclerotic ulcer before treatment with Hydergine; B) After 6 weeks of Hydergine therapy; C) after 6 months of treatment; D) After complete healing.

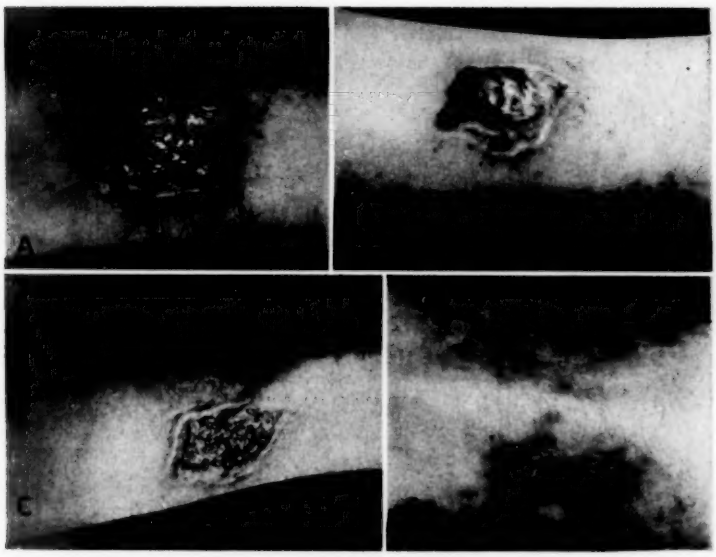

FIG. 3 (Case 3) A and B) Varicose ulcers of right and left legs respectively before beginning treatment with Hydergine; C and D) after 3 months of Hydergine therapy. Improvement in the dermatitis, as well as granulation of the ulcers, is apparent.

pated and the pulsations of the dorsalis pedis artery were only very faintly palpable. There was minimal cyanotic rubor of the toes when they were placed in a dependent position.

The treatment of this patient was on an ambulatory basis. He was given a 1-mg. tablet of Hydergine (CCK-179) t.i.d., a.c., and his ulcer was dressed with plain vaseline gauze. He noted gradual relief from coldness of his feet; granulation and epithelization of his ulcer progressed as indicated in Fig. 2, A, B, C and D. The original lesion as it appeared after débridement is shown in Fig. 2,A. The cyanotic borders of the ulcer which are apparent in Fig. 2,A, are no longer present in Fig. 2,B, which was taken after 10 days of treatment with Hydergine. The appearance of the lesion at the end of 6 weeks of treatment and at the end of 6 months, respectively, are shown in Fig. 2, C and D. At 7 months the lesion completely healed.

Case 3. (Ulcer of Venous Insufficiency). C. S., a white female, aged 74, in addition to her arteriosclerosis complained of varicose veins which had been severe for many years, and which had been treated 2 years previously by bilateral saphenous ligation. In spite of bed rest and conservative treatment at home, she had developed large painful ulcers and severe stasis dermatitis bilaterally. The lesions, as they appeared before treatment with Hydergine was begun, are illustrated in Fig. 3,A and B which show the right and left legs, respectively. A moderately severe, soft but non-pitting, type of edema was present bilaterally.

The patient was kept at bed rest for a month, during which time she was given 1 mg. of Hydergine t.i.d., a.c., combined with application of wet boric acid dressings to the ulcer; this treatment was continued for 8 days and then the boric acid dressings were replaced by vaseline gauze for an additional 3 weeks as the ulcer granulated. The Hydergine (CCK-179) was continued for an additional month. There was gradual subsidence of the edema during the period of treatment. Fig. 3, C and D show the lesions 3 months after beginning of treatment. Healing was complete and the dermatitis was also greatly improved at 4 months.

Summary: 1. Hydergine (CCK-179), a mixture of three dihydrogenated ergot alkaloids, dihydroergocristine, dihydroergocornine and dihydroergokryptine was given to seventy-two patients with peripheral vascular disease.

2. Significant improvement was noted in those patients with organic arterial peripheral vascular disease, particularly those with ulcerative lesions, but not in those with functional arterial involvement.

3. There was definite improvement in those patients with chronic venous insufficiency who had ulcerative lesions.

4. Toxic or side effects were rare.

5. It would appear that Hydergine (CCK-179) is a promising drug and deserves further study in the therapy of peripheral vascular diseases.

Since the healing of ulcerated lesions under treatment with Hydergine was good objective evidence of the effectiveness of Hydergine (CCK-179), a detailed description of 3 cases is presented, together with illustrations showing healing which resulted from oral treatment with the drug.

Addendum: Since submission of the manuscript, we have used the sublingual tablets, each containing 0.5 mg. of Hydergine, which are thought to be better absorbed.

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VITAMIN K CONTROL OF THE INCREASED HYPOPROTHROMBINEMIC EFFECT OF DICUMAROL IN CONGESTIVE HEART FAILURE

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THE treatment of thromboembolic disorders with dicumarol is receiving an increasingly prominent place in the field of medicine. Its greatest use has been in the treatment and prevention of peripheral deep vein thrombosis, intracardiac thrombosis, and pulmonary and peripheral embolism which commonly occur in conjunction with the cardiac disease. Patients with these conditions may have a considerable degree of congestive heart failure when treatment is instituted with the anticoagulants, and it is becoming increasingly apparent that a decreased tolerance to dicumarol is frequently present under these circumstances. Recently Stats and Davison[10] have demonstrated this increased hypoprothrombinemic effect of dicumarol in carefully controlled studies of a significant number of patients with congestive heart failure.

The application of anticoagulant therapy to the treatment of thromboembolic disorders necessitates that the prothrombin time be maintained within an optimal range. If it is thus maintained, hemorrhagic complications are not likely to occur and any new thrombus formation is unlikely to occur. If an increased hypoprothrombinemic effect is allowed to develop, hemorrhagic complications may appear, and if too vigorous corrective measures are then applied, the prothrombin level may return to the normal range and thromboembolic complications once more occur. If, in any manner, the dangerous hypoprothrombinemic effect can be prevented or altered so that a safer and predictable effect may be expected, then a much better application of anticoagulant therapy should be possible. This study is undertaken to reascertain the pattern of response to dicumarol of patients with congestive heart failure, comparing their response to that of normal individuals, and, further, to ascertain if daily administration of small doses of vitamin K might bring about a more normal pattern of response in the former.

Methods. The Quick method for determination of the prothrombin time was used in this study and is the standardized procedure in the laboratories of this hospital. The whole plasma determination was used exclusively. At least 3 determinations were done on each specimen of plasma and at least 2 of the resultant figures had to be within 0.4 seconds of each other before they were accepted. The average normal prothrombin time for this laboratory is 15.0 seconds with a range of $\pm$ 1.5 seconds.

For the purpose of this study a dicumarol tolerance test was set up. In this test the baseline prothrombin time is determined and then 200 mg. of dicumarol is administered to the subject. On each of the 3 following days at 24-hour intervals following the administration of the dicumarol another prothrombin time determination is

done. This procedure will be subsequently referred to as the 'Dicumarol Tolerance Test.'

The test was begun at varying times of the day. In the normal subjects it was started at the most convenient time. In the abnormals it was started as soon as the patient was deemed suitable for inclusion in the series, which, in most instances, was shortly after admission to the hospital. Irrespective of the time the test was started, however, every effort was made to obtain the subsequent blood specimens at as nearly 24-hour intervals as was possible. Overman, Newman, and Wright[7] performed carefully controlled studies and concluded that the time of day, the ingestion of meals, the type of diet, and the performance of moderate amounts of exercise did not significantly affect the prothrombin time.

Subjects. To the first group of 9 normal subjects the test was given in order to determine the pattern of response occuring with the use of the single dose of 200 mg. of dicumarol. These subjects did not have any demonstrable liver or renal disease.

The second group of 6 normal subjects was given the 'Dicumarol Tolerance Test' along with the administration, at 24-hour intervals, of 8 mg. tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester Synkayvite-Roche), the first dose being given at the time of the dicumarol dose. All cases in this group were also in the first group of normal subjects.

The third group of patients consisted of 14 abnormal subjects. All of these patients were seen immediately on admission to the hospital and were assayed for possible use in the study. All of those selected had moderate to severe right heart failure. The criteria used included a liver enlarged beyond that of normal size for the patient under consideration, peripheral edema of minimal to maximal degree, and other signs, present to a variable intent, of congestive heart failure. The patients were given 200 mg. of dicumarol without any other medication except for that used for the treatment of the congestive heart failure.

The fourth group consisted of 15 abnormal subjects selected under similar criteria, but given 200 mg. of dicumarol plus 8 mg. of Synkayvite, the first dose of the latter being given at the time of the dicumarol dose and continued at daily intervals for the duration of the test.

A fifth group of 15 normal subjects was studied in an attempt to determine an optimally effective dose of vitamin K_1 that could be used to produce similar effects as the 8 mg. dose of Synkayvite. The optimal dose was defined as one which would not depress the prothrombin time to a point where no reaction to the dicumarol could occur, yet an amount which would be large enough to prevent the increased hypoprothrombinemic effect of dicumarol in congestive failure. Doses ranging from 12 mg. daily down to 1 mg. daily were in these subjects.

Results. In the first group of 9 normal subjects (Table 1) the average response was 1.4 seconds. The greatest maximal response was 2.7 seconds. The time of the maximal response varied about equally between 24 hours and 48 hours after the single dose of dicumarol. All of the baseline prothrombin times were within the normal range except for one which was below normal. In this group 3 subjects experienced symptoms most likely due to the dicumarol, consisting of nausea, cramps and diarrhea. The figure of 3.0 seconds was chosen to represent the *maximal expected response* for the normal patient in the 'Dicumarol Tolerance Test.' An occasional normal patient will ex-

ceed this figure slightly as is demonstrated in the next group.

In the second group of 6 normal subjects (Table 2) the average maximal response to the dicumarol was 1.6 seconds. The greatest maximal response was 3.3 seconds which occurred in but 1 patient. The time of the maximal response averaged 48 hours from the single dose of dicumarol. The baseline prothrombin times for this group were all within the normal range.

In the third group of 14 abnormal subjects who had congestive heart failure (Table 3), the average maximal response to the single dose of dicumarol was 7.5 seconds, and the time of maximal response in all cases but two was

TABLE 1

		Prothrombin Times			*Maximum Response (in sec.)*	*Day of Maximum Response*
Case	*Baseline*	*24 hours*	*48 hours*	*72 hours*		
1	14.3	15.8	16.3	13.8	2.0	2
2	14.3	14.5	15.9	13.3	1.6	2
3	14.3	15.1	15.1	14.4	0.8	2
4	16.7	17.4	16.3	16.1	0.7	1
5	15.9	17.0	18.6	17.4	2.7	2
6	15.4	16.9	16.9	16.7	1.5	1
7	14.8	14.9	14.0	14.0	1.3	1
8	12.7	14.0	14.0	—	1.3	1
9	15.7	17.8	15.5	16.5	2.1	1

(These cases received only 200 mg. of Dicumarol on the starting day of the test.)

TABLE 2

		Prothrombin Times			*Maximum Response (in sec.)*	*Day of Maximum Response*
Case	*Baseline*	*24 hours*	*48 hours*	*72 hours*		
1	13.5	15.4	14.7	14.7	1.9	1
2	14.7	15.0	15.3	14.2	0.6	2
3	14.3	14.7	15.4	14.5	1.1	2
4	16.0	15.6	19.3	19.0	3.3	2
5	16.4	16.5	19.0	18.7	2.6	2
6	15.0	14.4	14.8	14.2	0.0	2

(These cases received 200 mg. of Dicumarol on the initial day and 8 mg. of vitamin K on each day of the test.)

TABLE 3

		Prothrombin Times			*Maximum Response (in sec.)*	*Day of Maximum Response*
Case	*Baseline*	*24 hours*	*48 hours*	*72 hours*		
1	20.2	20.5	24.8	23.6	4.6	2
2	15.8	18.4	20.4	18.1	4.6	2
3	24.0	28.2	54.0	—	30.0	2
4	17.4	18.4	18.4	17.5	1.0	2
5	16.6	16.1	16.2	16.2	0.0	—
6	16.4	21.9	33.5	30.3	17.1	2
7	15.5	16.8	18.7	15.4	3.2	2
8	16.0	17.5	19.2	18.3	3.2	2
9	15.2	20.3	33.5	28.5	18.3	2
10	19.0	19.7	21.2	17.4	2.2	2
11	18.6	17.8	19.3	16.6	0.7	2
12	17.7	19.8	19.2	16.6	2.1	1
13	15.8	23.0	30.9	23.7	15.1	2
14	15.9	19.4	18.3	16.2	3.5	1

(These abnormal cases received 200 mg. Dicumarol on the initial day of the test.)

at the 48-hour test following the initial dose of dicumarol. Seven subjects (50%) had baseline prothrombin times which exceeded the normal range. Nine of the subjects (64%) exceeded the maximal expected response.

In the fourth group of 15 abnormal subjects (Table 4) who received daily doses of vitamin K along with the dicumarol, the average maximal response was 2.3 seconds and the time of response after the single dose of dicumarol was about equally divided between the 24-hour and the 48-hour test. Five subjects (33%) had baseline prothrombin times which exceeded the normal range. Three subjects (20%) exceeded the maximal expected response.

TABLE 4

Case	*Baseline*	*Prothrombin Times*			*Maximum Response (in sec.)*	*Day of Maximum Response*
		24 hours	*48 hours*	*72 hours*		
1	13.8	14.0	14.7	—	0.9	2
2	17.6	19.4	19.6	20.4	2.8	3
3	15.6	16.9	15.2	16.9	1.3	1
4	15.4	16.6	17.0	15.7	1.6	2
5	15.0	15.7	18.1	16.5	3.1	2
6	21.6	22.6	17.7	18.0	1.0	1
7	13.9	15.4	16.7	16.4	2.8	2
8	24.3	33.9	30.1	25.6	9.6	1
9	13.2	14.2	13.5	14.4	1.0	1
10	18.8	17.9	17.5	17.3	0.0	–
11	14.1	15.0	14.3	14.2	0.9	1
12	14.9	15.5	14.6	14.8	0.6	1
13	15.9	17.5	16.4	15.6	1.6	1
14	16.2	22.3	18.4	17.6	6.1	1
15	17.9	19.8	18.7	—	1.9	1

(These abnormal cases received 200 mg. of Dicumarol on the initial day and 8 mg. vitamin K on each day of the test.)

Discussion. Saracbasi and Inceman[8] studied a group of 12 normal subjects to whom they administered 300 mg. of dicumarol 1 day and 200 mg. the following day. In none of their patients did they have a maximal lengthening of the prothrombin time to more than 5 seconds of the base level. This agrees well with our findings and our arbitrary maximal normal response of 3 seconds for the 'Dicumarol Tolerance Test' is felt to be well within the standard amount of deviation expected.

The group of normal subjects to whom vitamin K was given along with the dicumarol shows an average response which is equal to, if not very slightly greater than, the response obtained in the normal subjects given dicumarol alone. The findings in this group suggest that in normal individuals vitamin K is present in adequate amounts, and any additional vitamin K does not affect the 'Dicumarol Tolerance Test'.

Concerning the selection of the dose of 8 mg. of vitamin K which was used in this study, Allen and Julian[1] investigated a large series of patients with either extrahepatic or intrahepatic disease and prolonged prothrombin times. They attempted to determine the state of hepatic function by the response of the prothrombin time to doses of vitamin K. One of the drugs studied was Synkayvite and the daily dose used was 8 to 10 mg. They concluded that enough vitamin K was supplied by this dose to bring the prothrombin time down to normal within 24 hours if the function of the liver was adequate.

The demonstration of Groups 3 and 4 that the average response can be brought down from 7.5 seconds an average response of 2.3 seconds by the concomitant daily use of 8 mg. of water-soluble vitamin K suggests that, in some respect, there is a vitamin K deficiency in a number of these patients. Whether this represents a relative or absolute deficiency cannot be definitely ascertained at this time but the results seem to indicate that with the use of vitamin K a more optimal response to dicumarol can be obtained in patients who are in congestive heart failure.

There are 3 possibilities which might account for a deficiency of vitamin K. The first is a possible absolute deficiency of vitamin K in the gastrointestinal tract resulting from poor dietary intake. The second is poor absorption from the gastrointestinal tract due to passive congestion of the intestinal wall. The third is an abnormal response due to hepatic dysfunction brought about by the congestive failure, including also a certain degree of renal failure.

Uvnas[11] has made the statement that there are only four cases on record in which hypoprothrombinemia in man could be attributed to dietary deficiency. The fact is that it can be produced nutritionally in mammals only with marked difficulty since intestinal bacteria produce enough vitamin K for protection against K-avitaminosis. That there is adequate absorption from the gastrointestinal tract is demonstrated by this study inasmuch as oral dosage of Vitamin K has produced the desired results. The possibility, however, that there may be a deficient absorption of bile-soluble K salts from the intestine has not been proven. The depressed function of the liver may account for decreased bile excretion and this in turn for the partial vitamin K deficiency which has been suggested. However, the vitamin K given in this study was the water-soluble form and appears to be adequately absorbed from the gastrointestinal tract.

Cantarow[2] has demonstrated that there is depressed liver function in cases of congestive heart failure. Eleven out of 14 cases revealed abnormal bromsulfalein retention. White *et al.*[12] in performing needle biopsy studies on the livers of 30 cases of congestive failure demonstrated normal structure in 17 patients. The other 13 patients presented varying degrees and forms of hepatic pathology which could not be correlated with the type or degree of heart disease present. Felder *et al.*[5] in a study of 135 cases of chronic congestive heart failure found 74% had at least 1 abnormal liver function test out of 2 or more different tests performed on each patient, although only 30% of the total number of tests performed were outside the normal range. Again no correlation was possible with the type or duration of the heart disease. Shapiro *et al.*[9] concluded from their studies that patients with liver disease will respond to a small quantity of dicumarol only when the disturbance in the liver is sufficient to cause prolongation of the initial base-line prothrombin time.

These studies would indicate that varying amounts and degrees of hepatic disease are often present in patients with congestive heart failure. The amount of hepatic disease may, and often will, affect the prothrombin response to dicumarol. In this study, however, no correlation is possible between the results obtained and the degree of hepatic dysfunction, except insofar as prolongation of the initial baseline prothrombin time is concurred.

There were seven patients (50%) in the abnormal group who received the 'Dicumarol Tolerance Test' alone

(Table 3) who had prolonged prothrombin times initially and of these only 2 patients (14%) had an abnormal response. This is in contrast to an incidence of abnormal responses in 64% of the patients in the entire group. There were 5 patients (33%) in the abnormal group who received both dicumarol and vitamin K (Table 4) who had prolonged prothrombin times initially and only 1 of these (7%) had an abnormal response. This is in contrast to an incidence of abnormal responses in 20% of the entire group. The conclusion is that the presence of an initially prolonged prothrombin did not in any way predict an abnormal response. In fact, in the third group (Table 3), almost the opposite was true since every one of the patients (50%) who had a normal prothrombin time initially showed an abnormal response to the dicumarol. These results are in direct contrast to the work done by Shapiro *et al.*[9].

Mention should be made of the case in the fourth group who had the most marked maximal response to the dicumarol (Table 4, Case 8). This patient had advanced congestive heart failure and, in addition, gave a history of heavy alcohol consumption over many years. These factors may partially account for the marked response in this patient.

There seems to be no doubt in the minds of many authors that renal failure will enhance the hypoprothrombinemic effect of dicumarol. In this study no attempt was made to elucidate this problem, but one case (Table 4, Case 1) in group 4 had definite evidence of renal insufficiency (NPN 120 mg.) and yet exhibited a normal response.

There is a difference of opinion among contemporary writers concerning the relative advantages of water-soluble vitamin K and oil-soluble vitamin K_1 or K-oxide in the treatment of dicumarol poisoning[4,6]. This investigation suggests that water-soluble vitamin K is effective in attenuating the increased hypoprothrombinemic effect of dicumarol. The idea has been accepted that the same effects could be obtained with the use of the oil-soluble vitamin K_1. These studies were not done in abnormal subjects but, in the search for the optimal dose of vitamin K_1, the conclusion was reached that 4 to 6 mg. of vitamin K_1 given daily should produce results similar to those obtained with an 8 mg. dose of water-soluble vitamin K. This dose should not depress the prothrombin time sufficiently to prevent a response to the dicumarol but should obviate an excessive reaction.

Recent work published by Collentine and Quick[3] may shed light on the mechanism involved in the attenuation of the increased hypoprothrombinemic effect of dicumarol in congestive heart failure by water-soluble vitamin K substances. These investigators advance the hypothesis that vitamin K acts as a prosthetic group combining with an apoenzyme to form the active or holoenzyme responsible for the synthesis of prothrombin. This concept may be further extended by assuming that dicumarol likewise combines with the apoenzyme in such a manner as to prevent vitamin K from forming the holoenzyme. They demonstrated that K substances have a much greater affinity for the apoenzyme than dicumarol and that when a union with either has occurred, an excess of the other is necessary to supplant its opponent. We might thus postulate that the excess of K substance administered in this study is necessary for the formation and maintenance of an adequate amount of the true holo-enzyme in the presence of depressed hepatic function, thus contributing to the formation and maintenance of an adequate amount of prothrombin. If the excess of vitamin K

were not present, the inactive dicumarol enzyme would be formed in excess resulting in insufficient prothrombin formation and a state of dicumarol poisoning. It would appear that the relative affinity of vitamin K_1 for the apoenzyme is greater than is the affinity of water-soluble K substances since larger doses of the latter are necessary to produce the same anti-dicumarol effect.

Summary. 1. The increased hypoprothrombinemic effect of dicumarol in congestive failure is again proven experimentally by the use of the 'Dicumarol Tolerance Test'.

2. The increased hypoprothrombinemic effect of dicumarol in congestive heart failure can be modified by the use of water-soluble K substances given in a dosage of 8 mg. daily.

3. The anti-dicoumarin effect of vitamin K_1 is again substantiated. A daily dose to produce an effect similar to the water-soluble K substances is suggested.

4. A mechanism for this modification of the increased hypoprothrombinemic effect of dicumarol is postulated.

5. A discussion of the causes for the increased hypoprothrombinemic effect of dicumarol in congestive heart failure is presented.

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PENICILLIN TREATMENT OF CARDIOVASCULAR SYPHILIS

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IN our present state of knowledge, any evaluation of a new mode of therapy for cardiovascular syphilis is bound to yield inconclusive results. This frustrating eventuality is due to the many unsolved problems in the diagnosis of cardiovascular syphilis, and to the fact that the interpretation of the actual effects of the therapeutic measures under investigation cannot be appreciated fully because of the lack of suitable controls. This review is undertaken, therefore, with due cognizance of the tentative and relative character of the data presented, but, however, with the full conviction of the Reviewer that in penicillin, practitioners have at last a safe, effective means of supplementing the equally important medical aspects of treatment of cardiovascular syphilis.

Problems Involved in Evaluation of Treatment of Cardiovascular Syphilis. Among the still unsolved problems in the evaluation of penicillin therapy are the uncertain criteria of diagnosis, clinical or postmortem, of uncomplicated syphilitic aortitis; influence of race and sex on the outcome of treatment; the prophylactic effect of treatment in prevention of cardiovascular syphilis;

and the amount of treatment which is adequate in early syphilis to prevent the development of cardiovascular complications. Furthermore, insufficient time has elapsed to determine fully the efficiency of penicillin in the management of cardiovascular syphilis. A factor which makes evaluation of treatment on prognosis difficult is whether or not cardiovascular syphilis is changing with the passage of time, and that we are now seeing a different type of this phase of syphilis. The simultaneous occurrence in patients of cardiovascular syphilis with other aspects of late syphilis, such as neurosyphilis, may alter the picture of therapeutic efficacy, as well as increase the potential reactivity of the patient to a particular treatment system or drug. Other variable factors involved in evaluation of therapy which cannot be assessed accurately are: the presence of diabetes mellitus; hypertension; degree of arteriosclerosis; renal function, to mention only a few. It is not sufficient merely to use past records to obtain a control series against which to evaluate therapy in cardiovascular syphilis. This is unlikely if not impossible, since one cannot be certain whether patients in the previously treated group are similar to those who are to be subjected to the new method of treatment[14]. Furthermore, the attempts of groups of individuals or clinics to pool their results have also led to certain conclusions which are, of course, dependent upon the validity of such pooled results submitted for evaluation to a central set-up.

Barnett and Small[1], moreover, on the basis of a series of 334 cases of cardiovascular syphilis with aortic regurgitation, aneurysm, or both, attest to the statistical difficulties in the evaluation of the effect of antisyphilitic therapy in cardiovascular syphilis. They show that symptomatic and asymptomatic cases must be separated for study. In the former, cases observed for less than a year must be eliminated in order to obtain little- and much-treated groups of comparable initial severity. In the latter, no such elimination can be made, but the results must be expressed in relation to the total years of patient observation, rather than to the number of individual patients involved. Antisyphilitic therapy probably improves prognosis to some extent at any stage of cardiovascular syphilis, but it is definitely more effective when given before the onset of symptoms, and it probably becomes progressively less useful as the disease progresses. Along these lines, Flaum and Thomas[23] believe that the factors influencing prognosis of cardiovascular syphilis include: 1) the presence or absence of symptoms of diminishing cardiac reserve; 2) the size of the heart; 3) the age of the patient (arteriosclerosis); 4) the type of work performed; and 5) the amount of previous antisyphilitic therapy and when it was given in relation to the discovery of the cardiac involvement. Patients with cardiovascular syphilis respond to medical therapy better than was previously thought.

Involved also in the evaluation of cardiovascular syphilis therapy is the relative place of medical care, other than the so-called specific therapy in the therapeutic regimen. Although in this presentation, relatively little mention will be made of the various aspects of the so-called medical treatment of cardiovascular syphilis, it should in no sense indicate any lack of regard for the importance of this complementary treatment, especially of the new advances in this field. Furthermore, it is practically impossible to evaluate the relative importance of such treatment as compared with specific treatment, because no physician knowingly would resort in most cases

to medical treatment alone if his patient has definite evidence of cardiovascular syphilis. It is true, however, that some forms of so-called preparatory treatment for cardiovascular syphilis amount to practically no treatment at all.

Moore's[39] review of cardiovascular syphilis summarizes many of the problems involved in the determination of the effect of antisyphilitic therapy in this aspect of syphilis. In view of the uncertainty of diagnosis of uncomplicated syphilitic aortitis, information concerning the effect of antisyphilitic treatment must be sought from patients in whom the clinical diagnosis is as nearly as possible verified by the presence of aortic regurgitation, saccular aneurysm, or both. In this connection, Moore believes that only two methods of study seem applicable; the histopathology of aortic syphilis as affected by treatment and the clinical study of treatment effect.

The results of the study of the effects of therapy on the histopathology of the aorta, however, have yielded contradictory results. While Hood and Mohr[30] of Johns Hopkins Hospital found no histologic differences in the aortas of untreated and adequately treated patients, Howe[31] as well as Webster and Reader[61] found what appear to be definite differences in the two groups.

Moore points out that there are extraordinary difficulties in the way of accuracy in the second approach, that is, a clinical study of the effect of treatment in terms of symptomatic relief and prolongation of life span. The first clinical intimation of the presence of cardiovascular syphilis may be sudden death, or an attack of congestive heart failure which is fatal in a few days or weeks. In such cases, there is no way in which to estimate the value of specific treatment, since there is no time to give it. Because the Johns Hopkins material contains nearly one-third of the cases of cardiovascular syphilis in this category, Moore and his group eliminate, from statistical consideration of treatment effect, all patients who died within one year of the onset of symptoms. Furthermore, since in a given patient, the course of the disease is wholly unpredictable with or without therapy, conclusions may be drawn only from large numbers of individuals and in terms of averages. Aortic regurgitation, saccular aneurysm, or a combination of the two, are usually fatal in the long run from progressive inflammation or from the vicious circle of mechanical circulatory defect, unless the patient dies of an unrelated process.

The practically uncontrollable factors of the economic situation and of physical work are related to mechanical circulatory death. A sedentary occupation is essential to prolong life to the maximum in a patient with aortic aneurysm or regurgitation. The factor of work stress is, according to Moore, of as great or more importance in prolonging life as is antisyphilitic treatment, and account must be taken of it in a statistical analysis of results. Because of the more strenuous occupations of males, sex plays an important role in prognosis. Moore rates the race of the patient as an important factor in prognosis. For example, syphilitic heart disease is not only more frequent in the Negro than in the white, but it is probably also more rapidly progressive. The duration of infection and age of the patient are undoubtedly also involved in prognosis. The probably prolonged symptomless course of aortic insufficiency and aneurysm is an item of greatest significance in an estimate of the results of treatment. An estimate of the effect of antisyphilitic treatment can be had only by comparison of

groups of patients who received one or another type or amount of specific therapy with another group which received none at all. The purely medical management of the several groups must be so far as possible identical. If the purity of the experiment is to be maintained, the physician must resist the temptation to try another form of antisyphilitic therapy if one fails to bring about symptomatic relief, or if symptoms recur. Finally, for complete statistical accuracy, Moore suggests that the results of treatment should be expressed only in patients followed until death, and if possible with verification of the diagnosis by necropsy. It is only at death that life span can be measured.

The Results of Metal Chemotherapy in Cardiovascular Syphilis. Moore's summary of this problem is so satisfactory that it is quoted as a background for comparison with penicillin therapy of this phase of syphilis.

"These complexities are cited in extenuation of the fact that now, nearly 40 years after the first introduction of salvarsan by Ehrlich and the initiation of effective metal chemotherapy, there are available in the world literature only 3 comparable, and reasonably statistically reliable studies of the effect of antisyphilitic therapy in cardiovascular syphilis. These are by Grant, Padget and Moore, and Stratton."

"Depending on the biostatistical method employed, even Grant's data are not strictly comparable with the other two series. Based on 171 cases of aortic regurgitation followed for 10 years or until death, Grant indicates that the mortality rate is higher, and especially so from cardiovascular syphilis, in patients untreated or inadequately treated (with potassium iodide only) than in those given something approaching reasonable arsenic and heavy metal therapy; and that the proportion of patients still living 'uneventful and unchanged' after 10 years is higher in the treated group. If, however, one re-analyzes Grant's material on the basis of average duration of life after onset of symptoms, limiting the analysis to patients already dead, there is no difference in the two groups (89 months in 29 treated patients, 87 months in 89 untreated patients). The average duration of life in Grant's untreated group is greater than in treated patients in the two American series. There is, however, a significant difference in the clinical material. Grant's patients were all white males, British Army pensioners, who were able to lead an essentially sedentary life. In the two American series, the patients are predominantly Negro laborers, in whom the unfavorable influence of hard physical work is repeatedly evident."

"The data of Padget and Moore and of Stratton, combined and refigured to show the average duration of life in 60 patients with saccular aneurysm (32 untreated, 28 treated) and 91 patients with aortic regurgitation (51 untreated, 40 treated), all of whom lived at least one year after the onset of symptoms or recognition of the lesion, but all of whom were dead at the time of study, indicate that life span may be approximately doubled by the factor of treatment. The actual figures are for aneurysm untreated, 41 months, treated 74 months; aortic regurgitation untreated, 45 months; treated, 75 months."

"The data of Reader and his associates cannot be compared for lack of pertinent information, but also strongly suggest that antisyphilitic treatment is effective in prolonging life."

"All these results were obtained with prolonged cautious treatment with arsenic, bismuth and mercury, as outlined in Chapter 18 of my monograph,

"The Modern Treatment of Syphilis'."

Therapeutic Shock and Paradox. In the conventional therapy of cardiovascular syphilis, two concepts, therapeutic shock and therapeutic paradox, played an important role in the planning of therapy for this phase of the disease. Full discussion of these problems is made in "Modern Clinical Syphilology," and in the paper by Stokes, Wolferth, Edeiken, Falk, and Ford[56] and others[38,5]. We shall outline the salient features here. The former, commonly spoken of as the Jarisch-Herxheimer or Herxheimer reaction, is a flare of the disease upon the institution of treatment. Originally described by Jarisch for the secondary eruption under treatment with mercurial inunction, it has been identified in every observable phase of syphilis, early and late. In the use of the arsenicals its intensity up to the point of destructive violence probably depends in part upon the initial intensity and impact of the treatment, though the "allergic" status of the individual also participates in this reaction. Dosage, as well as the activity of the treatment agent used, both play a role in its production. Its mechanism is still unknown, but the earlier attributing of the flare to lysis of Treponema pallidum at lesion sites is certainly untenable, since the reaction appears after the use of relatively nonspirillicidal drugs, for example, mercury and tryparsamide, and can be seen in lesions of late syphilis in which treponemes are few and far between. It is more probable that at least a part of the reaction is in the cellular tissues and of the nature of an immunity response, or even an allergic reaction. Therapeutic shock induced by metal therapy had to be controlled. This was accomplished by two devices: initial low dosage, and the preliminary use, before the more shock-producing arsenicals were administered, of more or less prolonged "preparation" with the slower-acting heavy metals, although bismuth itself may produce therapeutic shock, and neoarsphenamine can be given without serious clinical shock if the dosage is low enough.

Clinically the Jarisch-Herxheimer reaction may be manifested by increased body temperature as well as by a flare-up of obvious or subclinical syphilitic lesions immediately following treatment with anti-syphilitic agents. In the heart this could result in serious embarrassment. Therapeutic shock, then, has been accepted as a danger in the treatment of cardiovascular syphilis during the middle and later years of the arsenical era, and has discouraged the full use of our therapeutic resources against syphilis in treating the disease in the heart and great vessels. On the other hand, the vasculotoxicity of the arsenicals as such should not be confused with the Jarisch-Herxheimer reaction.

Wile[65] first described therapeutic paradox as the conception that the patient might be injured even fatally by rapidly induced healing of a syphilitic lesion in a vital structure. This was originally observed in the liver. Syphilitic hepatitis improved rapidly under the arsphenamines, and then with equal rapidity the patient went downhill to uncontrollable ascites, with other evidence of hepatic injury, portal obstruction and death. Later the concept was broadened to include other late manifestations of syphilis, and supposed fibrous contractile scarring as a phase of the healing process, with shrinkage and distortion of the involved structure, rather than lack of time for functional adjustment, was emphasized as the evil consequence. The mechanism of the therapeutic paradox is unknown. It may be prevented much in the same way as thera-

peutic shock. Even substitution of a less toxic arsenical (arsenoxide) may, because of lessened vasculotoxicity, yield fewer therapeutic paradoxes than the arsphenamines.

Sources of Pertinent Information. For the student of the treatment of cardiovascular syphilis, a number of good sources of information are available. Among these are: Stokes, Beerman and Ingraham[55], Fleming[25], Kampmeier[34], Cole and others[9], Hinrichsen[29], Woodruff[68], de la Chapelle[12], Nicol[43], Cormia[10], Eisenberg[20], Chapman and Morgan[7], Prebble[49], Webster[60], Barnett and Small[1]. Particular reference to the material contained in these sources relating to the therapy of cardiovascular syphilis with penicillin will be made in appropriate places. In addition, many of the papers dealing with the actual treatment of cardiovascular syphilis with penicillin contain considerable information dealing with the fundamental aspects of the therapy of cardiovascular syphilis.

Penicillin in Cardiovascular Syphilis. Since penicillin is a fast-acting spirillicide, and should theoretically behave like other fast-acting spirillicides, the arsphenamines, it could produce not merely a febrile reaction, but an overall exacerbation of the syphilitic process, transient and serious in proportion to the vital location of the lesion and the size of the initial dose. Early in the penicillin era, workers attempted to control anticipated shock effect by reduction in dosage, but the observation of Olansky[44] seemed to indicate that reductions in dosage to as low as 1,000 units were without effect in preventing Herxheimer reactions, though their intensity might conceivably be reduced. Tucker and Farmer[58] showed that a febrile Herxheimer reaction fails to appear only below such small doses as 1 to 10 units per kilogram of body weight. One-tenth of the dose that will render a syphilitic lesion darkfield negative is capable of causing a Jarisch-Herxheimer reaction. Purified Crystaline G penicillin appears to yield fewer severe local flares and immediate serious reactions as compared to the arsphenamines. While this fact has encouraged certain groups (notably at the University of Pennsylvania) to make a complete study of the effects to cardiovascular syphilis, other investigators have been extremely conservative in their exhibition of a rapid-acting drug like penicillin in patients with cardiovascular syphilis. (Wile[66]; Peralta and Castaneda[46]; Tung[59]; Eisenberg[20]; Blomquist[3]; and Willcox[67]). For example, Wile cautioned us against the use of too intensive methods in the treatment of cardiovascular syphilis. He felt that after the disease has reached a clinical horizon, treatment reactions are more apt to occur. This relates to either the arsenicals or penicillin, both of which are fast-acting drugs. This point of view seemed somewhat justified at first because in a disease process, such as cardiovascular syphilis, where sudden death, with or without treatment, is frequent, treatment with even small doses of penicillin seemed to be unsafe. Early reports, although admittedly equivocal, featured reactions, even fatal, in patients with cardiovascular syphilis under penicillin therapy[16,6,39,52,48]. Subsequent experience by many groups and in a reasonably large series of cases indicates that not only is penicillin well tolerated but may, within the limits of analysis previously described, actually induce improvement in the patient from the standpoints of relief of symptoms and prolongation of life. These data obtained from the literature have been tabulated for the sake of brevity in chronologic order in the following Table.

TABLE 1.—PENICILLIN TREATMENT OF CARDIOVASCULAR SYPHILIS

Author & Date	*No. of Patients*	*Diagnosis*	*Therapy*	*Reaction*	*Remarks*
Dolkart and Schwemlein[18] 1945	2	Aortitis with dyspnea and precordial pain	*Patient 1*—Daily injection of penicillin *Patient 2*—700,000 u. penicillin in doses, 20,000 u. every 2 hours	*Patient 1*—On third day after 60,000 u. penicillin, 4 original attacks. 4th day, 60,000 u. (in 3 doses), 7 anginal attacks with frequent extra systoles *Patient 2*—Precordial pains after 700,000 u. penicillin	Penicillin should not be used in cardiovascular syphilis because of reactions
Morginson[42] 1946				Jarisch-Herxheimer reaction to penicillin indicated efficacy. May be avoided by lowered dosage	Advised against use of penicillin in cardiovascular syphilis
Hill[28] 1946				No adverse effects	
Russek, Cutler Fromer and Zohman[50] 1946	15	Aortitis (4 had aortic aneurysms)	Penicillin, 40,000 u. every 2 hours for 85 doses	One patient had mild substernal pain on third day of therapy. Continued on treatment uneventfully	Jarisch-Herxheimer is uncommon. Therapeutic paradox is rare
Moore[40] 1946	12	Aortic regurgitation, aortitis with osteal stenosis aneurysm (6 had neurosyphilis)	Penicillin started in small doses	One patient with large aneurysm of thoracic aorta died of rupture 6 months after treatment	1 possible therapeutic shock. Patient died on 4th day. Combined penicillin and malaria. Denies existence of therapeutic paradox. Risk of therapeutic shock greatly exaggerated
Callaway *et al.*[8] 1946	1	Aortitis and Neurosyphilis	Penicillin	Rupture of aortic cusp 10 days after completion of penicillin therapy	
J. Am. Med. Assn.[33] 1947					Penicillin will cause Jarisch-Herxheimer reaction and therapeutic paradox in cardiovascular syphilis
Dennie and Dwyer[15] 1947			Prepare patient with 6–12 injections of bismuth, and daily potassium iodide before penicillin which is to be given in gradually increasing doses. Conclude with one year or more of bismuth therapy		
Tucker and Farmer[58] 1947	30 (34)*	22 (25)* aortic regurgitation. 8 (9)* thoracic saccular aortic aneurysm	Penicillin started in doses ranging from 500 to 100,000 units every 3 hours in total	5 patients had temperature rise 37.8 and 39.0 during penicillin therapy (had neurosyphilis). 2 with angina attacks prior to therapy, had attacks during and after the therapy. No changes in blood counts, sedimentation rates and electrocardiogram	Not sufficient evidence to prove previously reported cases died of therapeutic shock

* Observed 4 additional patients (1 with aneurysm and 3 with aortic insufficiency) after study was submitted for publication

Chapman and Morgan[7] 1947	No data	Aortic aneurysm	Penicillin. Initial dose of 10,000 units followed by 15,000 units at 2 hour intervals. Total dosage 6 million units Potassium iodide orally and bismuth intramuscularly every other day during the course of treatment	No reactions	
Syphilis Study Section, National Institutes of Health[57] 1948					Since small doses of penicillin produce Jarisch-Herxheimer reaction in early syphilis, it should be avoided in cardiovascular syphilis
Woodruff[58] 1948			Advises bismuth before penicillin		
Porter[18] 1948	6	Cardiovascular syphilis	Penicillin	No reactions. Decompensation which was present before became worse during therapy, but was controlled medically	5 of 6 patients improved symptomatically. One with thoracic aneurysm died of rupture of aneurysm 2 days after 9.6 million units penicillin
Kossman and Flaum[35]	49	Cardiovascular syphilis (11 had no previous treatment)	Penicillin	One patient had recurrent attacks of precordial pain during therapy. Another had paroxysmal dyspnea. Both had congestive failure, and one complained of angina prior to treatment	
Peters[47] 1948	about 20	Cardiovascular syphilis with coexisting neurosyphilis	Aqueous penicillin. Some cases started on 5,000 u. Dose gradually increased to 10,000; 20,000; 30,000; 40,000 u. every 3 hours, total 6 million units. Others 40,000 u. every 3 hours to total 2.4 million units	Few complications	
Eisenberg[20] 1948	about 20	Uncomplicated aortitis	Penicillin oil-beeswax. Initial dose 100,000 u. Increase by 100,000 u. after the third and fifth day to 300,000 u. Total dose 4.5 million u. in 15 to 20 days	No untoward reaction	
Webster and Reader[61] 1948			Penicillin. 20,000 u. every 3 hours, or 300,000 daily for two weeks (preferably procaine penicillin followed by 300,000 u twice a week for next 10 weeks		Hazard of therapeutic shock and paradox is hypothetic
Scott, Maxwell and Skinner[52] 1949				Death of patient from rupture of aneurysm 49 hours after penicillin had been started for meningococcus meningitis	

TABLE 1.—PENICILLIN TREATMENT OF CARDIOVASCULAR SYPHILIS—(*Continued*)

Author & Date	*No. of Patients*	*Diagnosis*	*Therapy*	*Reaction*	*Remarks*
Peralta and Castaneda[36] 1949	25	2 aortic insufficiency (1 acute cardiac insufficiency), 2 aneurysm, 1 myocarditis, 1 coronary stenosis (infarct) aortitis and coronary arteritis	Penicillin G 2,500 u. initial dose. 50,000 to 100,000 in non-coronary cases. Total 4.5 to 8.0 million u.	28% of patients had symptoms during therapy. 3.9% had precordial pain. 7.8% had electrocardiographic changes without symptoms during treatment (disappearing later). 1 patient died of cardiac insufficiency 1 month later	
Flaum and Thomas[24] 1949	39	30 aortitis (insufficiency) 9 aortic aneurysm (8 no previous therapy). Additional group of 22 patients in above, syphilis of the cardiovascular system was suspected and treated with penicillin (not included in study)	All but 3 had 3 injections of bismuth preceding the penicillin (30,000 to 50,000 u. every 3 hours to a total of 3 to 6 million u.) 3 patients received penicillin in oil beeswax, 300,000 to 600,000 u. a day to totals 4.2, 7.2 and 9.0 million u. respectively	No reactions *per se*. 2 patients admitted with cardiac failure, died in failure, one 5 weeks and the other 2 months after therapy	No danger of therapeutic shock, but believe patients should be prepared with 0.2 gm. bismuth every 5 days for 3 doses
Russek, Nicholson and Zohman[30] 1949	78 males 35–58 years	9 aneurysms; 10 coronary ostial stenosis; 1 congestive failure	58 received 40,000 u. penicillin for 85 doses. 20 received 600,000 u. penicillin in oil for 6 doses	No Jarisch-Herxheimer reactions. 1 patient had attack of substernal fever during therapy. He had had similar attack prior to treatment. Patient in congestive failure died 1 week after completion of treatment	Jarisch-Herxheimer reaction, in cardiovascular syphilis, if it occurs at all, is rare
Falk, Edeiken, Ford and Stokes[21] 1949	12	In decompensation	Medical therapy concurrent with penicillin G 500–40,000 u. every 2 hours to total of 4.8–9.6 million u.	2 had rise in temperature from 6–16 hours after first penicillin injection	All improved. Penicillin plus medical better than the latter alone
Edeiken, Falk and Steiger[17] 1949	50	23 with aortitis; 20 with aortic insufficiency (18 with neurosyphilis); 5 with aortic aneurysm and aortic insufficiency	Penicillin, 1.2–9.6 million u. 40 of the patients had received previous therapy, 4 as recently as 3 months prior to receiving penicillin	4 of aortitis patients had rise in temperature during treatment. One had angina 10 months after completing treatment. 3 aortic insufficiency cases and temperature rise. No pyrexia among aneurysm patients	8 patients had electrocardiographic changes during therapy. 6 patients with decompensation did well. No therapeutic paradox observed

Moore[39] 1949	31	6 aneurysm; 25 aortic regurgitation	21 survivors followed 158–1243 days (average 567 days, or 18 mo.). 15 never in failure before penicillin. None since. 6 in failure prior to treatment 3 doing well—2 with aneurysm dead (15 and 158 days after treatment). 4 living 429–773 days. 4 of aortic regurgitation died 21–499 days after treatment		
Flaum[22]	55	Cardiovascular syphilis	19 not previously treated. 12 were given preliminary bismuth. 7 not treated with bismuth. 28 of 36 patients who had received previous therapy 1 or more years prior to admission. 4 of these were given bismuth (1 to 3 injections) prior to penicillin	No data	No adverse reactions. 5 had fleeting presternal pain. 2 had nocturnal paroxysmal dyspnea. All 7 had aortic insufficiency
Diefenbach[15] 1949	1	Aneurysm	Penicillin. 3 days of treatment	Expansion of aneurysm. Occlusion of left bronchus and death	
Hayward[27] 1949		Aortitis aneurysms	2–3 months preparation with bismuth and iodides previous to 8–10 million u. penicillin in 10 days		Herxheimer reactions are uncommon
Coale, Allen and Delp[8] 1950	70	48 aortitis; 18 aortitis with insufficiency; 4 aortic aneurysm	47 previous therapy; 23 no previous therapy. Penicillin. 6 million u., 600,000 u. per day for 6 days (except Sunday), then 400,000 u. daily for 6 days. (4 of patients received 10 to 15 million units)	2 with neurosyphilis developed fever during treatment	Penicillin is safe. No necessity for preparatory treatment with bismuth and iodides
Edeiken, Ford, Falk and Stokes[18] 1950	12	Cardiovascular syphilis in congestive failure	4.8–9.6 million u. penicillin (2 cases were started on 500 u. doses, 8 on 10,000 u., 2 on 40,000 u. every 3 hours). Duration of treatment 12–15 days	No untoward reactions, except febrile reaction in 2. 2 deaths, cause undetermined	All improved. Penicillin plus medical treatment better than latter alone
Leech[36] 1950	17	5 uncomplicated aortitis; 7 aortic insufficiency; 1 aortic insufficiency and aneurysms of ascending aorta; 1 aortitis, probably aneurysm; 3 patients with syphilis and probably nonsyphilitic cardiovascular disease; 2 patients had no previous therapy	Penicillin oil beeswax, 300,000 u. per day for 20 days (600,000 u. on Saturday, none on Sunday)	3 patients died, but death was not related to penicillin	Penicillin alone is good treatment. No need for preparatory treatment

TABLE 1.—PENICILLIN TREATMENT OF CARDIOVASCULAR SYPHILIS—(*Continued*)

Author & Date	*No. of Patients*	*Diagnosis*	*Therapy*	*Reaction*	*Remarks*
Weir, Roberts and Tullis[62] 1950	43	31 aortic insufficiency without aneurysm; 6 with aneurysm, 1 aortitis, 3 aortic insufficiency with aneurysm, 2 not stated	Preparatory, penicillin G in beeswax and peanut oil, procaine penicillin G in peanut oil, crystalline penicillin G in sesame oil with 20% aluminum monostearate. 400,000 or 6 million u. per day (1 dose) for 15 days. (⅛, 6 million; ⅛, 9 million u.)	16% had febrile Jarisch-Herxheimer reactions, not severe in 16.8% of patients	Therapeutic shock and paradox have been overemphasized
Forsey[26] 1950	From 161 cases (25 aortitic insufficiency; 11 aneurysm valid)		Penicillin	No case of serious reaction	
Sinclaire and Webster[53] 1951	53	9 aortitis (6 previous therapy), 36 aortitic regurgitation (20 had previous treatment), 8 aortitis and saccular (7 had previous treatment) aneurysm	2–12 million units penicillin	No therapeutic paradox. 2 aortitis had Jarisch-Herxheimer reactions (febrile). 4 aortitic regurgitation had Jarisch-Herxheimer reactions. All patients with reactions also had neurosyphilis	2 of aortitis died 1 month and 2 years after treatment (non-cardiac). 6 aortitic regurgitation died 2 months to 3 years after treatment. (4 cardiac, 2 non-cardiac deaths.) Penicillin alone is treatment of choice in cardiovascular syphilis
Flaum and Thomas[23] 1951	69	Aortic insufficiency and/or aneurysm	Procaine penicillin in oil with 2% aluminum monostearate, 600,000 u. dose daily, every other day or 3 times a week for 10 doses	No adverse reactions	Danger of therapeutic shock is greatly exaggerated
Edeiken, Ford and Stokes[19] 1951	61 additional cases (111 in whole series) (50 or 46% had neurosyphilis); 48 aortitis; 51 aortic regurgitation; 9 aortic regurgitation with aneurysm, 3 aneurysm		Recent scheme, procaine penicillin ambulatory, 600,000 u. in a single injection daily for 10 days (Total 6 million u.)	No serious reactions in entire series. No unequivocal example of therapeutic paradox	
Bruetsch[4-10] 1951		Cardiovascular syphilis	Penicillin 25 million u., 400,000 to 600,000 u. a day		Occurrence of untoward reaction in cardiovascular syphilis has been overemphasized
Wheeler and Curtis[63] 1951	21	Cardiovascular syphilis. 13 previously untreated. 8 previously inadequately treated. All but 5 symptomatic	Penicillin dosage varied widely, 12–40,000 u. aqueous penicillin G every 3 hours for 100 doses (4 million u.)	10 patients eliminated from evaluation of reaction. Of remaning 11, 3 febrile rise within 24 hours after starting penicillin. (2 of these had inactive paresis 2 possible examples of therapeutic paradox	No need to prepare patient with iodides or bismuth
Johnson and Shapiro[32] 1951	17		Penicillin G. Total dosage 4,008,000 u. Injections 3 times a day. 1,000 u. first day. 2,000 u. second day. 3,000 u. third day. 5,000 u. fourth day	10,000 u. the fifth day. 20,000 u. the sixth day, 30,000 u. the seventh day, 40,000 u. thereafter. No febrile reaction	

Packer[48] 1951	60	Aortic regurgitation	Penicillin. Schedule similar to neurosyphilis	No mishaps	See Weir, Roberts and Tullis 1950
Willcox[67] 1951					Preparatory bismuth and iodide used by British physicians
Whorton and Denham[64] 1951	1	Gummatous syphilitic aortitis	Sodium penicillin. 140,000 u. every 3 hours	Patient died suddenly 27 hours after therapy was begun	Jarisch-Herxheimer reaction is uncommon. Cause of death undetermined
Lian, Nedey and Cassimatis[37] 1951	24	Aortitis—19 with insufficiency, 2 with aneurysm, 3 with insufficiency and aneurysm	6 injections of aqueous penicillin daily for 10–15 days. Initial dose 200,000 to 1,000,000 u., total dose 3,000,000 to 15,000,000 u. Several patients had repeated courses	2 patients died, 1 on third day of penicillin treatment, 1 on third day after therapy was terminated (Both not due to penicillin. No Herxheimer reactions. Some slight febrile reactions	Advise preparatory medical therapy as if the patient were nonsyphilitic. Use penicillin only if treatment fails. Also suggest few mercury cyanide and bismuth injections and repetition of course if necessary
Prebble[49] 1951			After* preparatory treatment, procaine penicillin with 2% aluminum monostearate, 600,000 u. Total dosage of not less than 12 million u. Rest 1–2 months followed by alternate courses of bismuth once a week for 10 to 12 injections. Rest 1 month, then penicillin (another 600,000 u. per day to a total of 12 million units)		Preparation with iodides orally or intravenously (10–12% sodium iodide) Bismuth oxychloride 0.2 gm. (total of 12 each) given twice a week
Stokes, Wolferth *et al.*[56] 1951	111 cases observed from about 3 months to about 58 months following therapy	48 uncomplicated aortitis; 51 aortic insufficiency; 9 aneurysm and aortic insufficiency; 3 aneurysm	Earliest cases aneurysms, penicillin, but mostly with crystalline penicillin G 40,000 to 80,000 u. every 2 hours to a total of 4.8 to 9.6 million u.	No unequivocal cases of therapeutic paradoxes. Little evidence of therapeutic shock	Advocate 2 hour schedule crystalline penicillin G, 40,000 to 80,000 u. total of 9.6 million u. or 600,000 or 300,000 u. procaine penicillin single or 2 a day injection schedule respectively to total 6 million u.
Curtis *et al.*[11] 1951			Penicillin daily or two times a week for 5 weeks. 10 injections of 600,000 u. penicillin aluminum monostearate each for a total of 6 million u. Course may be repeated 2–3 times		
Butterly and Fishman[5] 1952	1	Syphilitic aortitis. Coronary ostial involvement	300,000 u. penicillin for upper respiratory infection	6–8 hours after injection developed cough and chest pain. Died 3 days later	Autopsy proved presence of syphilitic aortitis with coronary ostial involvement
Mohr and Hahn[38] 1952	4	Neurosyphilis—no cardiovascular involvement before treatment	Varying amounts with or without fever	6–18 mo. after treatment all 4 developed aortic insufficiency	Not certain whether these are therapeutic paradoxes

Jarisch-Herxheimer Reaction and Therapeutic Paradox (Penicillin Therapy). From the compilation of the literature on penicillin therapy of cardiovascular syphilis, it is apparent how groundless are the fears originally expressed that this mode of treatment would be productive of an excessive number of therapeutic shocks and paradoxes. In fact, Moore, Farmer and Hoekenga[41] as early as 1948 felt that in cardiovascular syphilis the febrile response of the Herxheimer reaction was observed rarely, and then only in patients with an associated neurosyphilis were there active cerebrospinal fluid findings. They observed no clinical suggestion of increased cardiovascular damage, nor could any evidence of this be detected by serial electrocardiograms, leukocyte counts and sedimentation rates. The Johns Hopkins group believed that "the risk of a serious Herxheimer reaction in cardiovascular syphilis has been grossly exaggerated."

In a recent report, Wheeler and Curtis[63] of the University of Michigan, analyzed the reported deaths and reported reactions as follows:

"Of the 8 possible reactions, there are reported 3 fatalities. The patient reported on by Porter had received 4 months of bismuth and iodide therapy before penicillin was administered. Two days after 9.6 million units of penicillin had been given the patient died of rupture of a huge aneurysm. It was evident before treatment that rupture of this aneurysm was imminent and it is impossible to say whether treatment had anything to do with the course of events. In the case presented by Moore the cause of death was likely cardiac failure which developed on the fourth day of treatment. The aorta was filled with plaques of syphilitic aortitis each of which contained fresh hemorrhage. Evaluation in this instance is complicated by the patient's being treated with malaria as well as penicillin. Scott and Maxwell's patient suffered from purulent meningitis of unknown cause. Response to penicillin seemed satisfactory, but the patient died suddenly during convalescence of rupture of a previously unsuspected aneurysm. The possibility of bacterial involvement of the vessel was not discussed."

"Of the 8 possible reactions there are 5 reports indicating temporary interference with cardiac function. One of Porter's 2 patients had received 2 weeks and the other had received 2 months of potassium iodide and bismuth therapy before penicillin was given. Each had aortic insufficiency and one also had an aortic aneurysm. Both were in congestive failure before penicillin was given. As good 'compensation as possible' was obtained by use of digitalis, diuretics, and bed rest. Each developed increasing evidence of congestive failure 2 weeks after penicillin was begun. Each responded satisfactorily to diuretics and greater curtailment of activity. The observation that congestive failure associated with syphilitic aortic insufficiency may be refractory to treatment and that it tends to recur casts some doubt on the conclusion that these patients present evidence of the therapeutic paradox."

"Dolkart and Schwemlein's first patient was seen in 1941, at which time diagnoses of latent syphilis and rheumatic heart disease with mitral stenosis and aortic stenosis were made. From 1908 to 1935 the patient had received an unknown amount of arsenic and bismuth. During 1942, an aortic diastolic murmur became evident. On two occasions in 1943, the patient was hospitalized because of chest pain and dyspnea. In 1944, he was again hospitalized and treated for congestive failure. In the summer of 1944, anginal

pain on strenuous effort was noted. During 1942 and 1943, 50 doses of bismuth were given. The patient was rehospitalized in September, 1944, for penicillin therapy. Ten thousand units of penicillin given on September 24th produced no reaction. After 20,000 units on September 25th, the patient noted 4 episodes of anginal pain. Twenty thousand units were given again on September 25th and 20,000 units 3 times on September 26th. Seven episodes of anginal pain were noted on September 26th and ventricular extrasystoles appeared on physical and electrocardiographic examination. The penicillin was stopped. The extrasystoles disappeared. Because of the associated rheumatic heart disease, the amount of pretreatment, the evident cardiac dysfunction before penicillin was given, it is hazardous to claim that this is an example of a Herxheimer reaction."

"The second patient reported by Dolkart and Schwemlein was given penicillin for an upper respiratory infection. After 700,000 units given over a 3-day interval, precordial pain appeared. The penicillin was stopped and the pain disappeared by the following morning. This patient had aortic insufficiency and tabes dorsalis, the diagnosis being made in 1936, nine years before penicillin therapy. From 1936 to 1939, he was given intermittent treatment consisting of iodides, bismuth, and neoarsphenamine. In 1938 and 1939, several episodes of precordial pain had occurred, but the patient denied precordial pain from 1939 to 1945. He also denied knowledge of syphilis or of specific treatment for it. Besides a possibility that the history was unreliable, the reappearance of the precordial pain at the time of penicillin therapy may have represented only coincidence. It might even be that the pain was tabetic."

"The report of Callaway and his associates concerns a 42-year old carpenter who received penicillin in the treatment of neurosyphilis. At the time of treatment compensated aortic insufficiency was observed. No reaction during therapy was noted. When the patient returned to work 10 days after therapy, precordial pain appeared. The pain was progressive. About 6 weeks later the patient went into congestive failure. The murmur had taken on a harsh quality suggestive of a ruptured aortic cusp. Treatment for congestive failure restored compensation but the cardiac reserve was too low to permit the patient to return to work. Rupture of a valve was not proved by autopsy. In the event of valve rupture, it is unlikely the patient could regain compensation. It is impossible to prove whether the breakdown of cardiac reserve was a result of the penicillin therapy or whether it represented a natural progression of the disease."

"A review of the present literature dealing with the use of penicillin in cardiovascular syphilis indicates that about 190 cases have been reported. About 35 of these patients carry diagnoses of uncomplicated aortitis. Since a diagnosis of uncomplicated aortitis is subject to considerable possibility of error, results pertaining to this group of patients should be accepted with reserve. The remaining 155 patients present evidence of either aneurysm, aortic insufficiency, or both, and as such permit diagnoses of cardiovascular syphilis. Of this latter group, approximately 130 patients have been given varying amounts of iodide and metal therapy before penicillin administration, and about 25 have received no pretreatment before penicillin therapy. In no instance has an unques-

tionable adverse reaction to penicillin therapy been recorded."

Whorton and Denham[64], who reported the occurrence of a possible Jarisch-Herxheimer reaction after penicillin treatment in a patient with gummatous syphilitic aortitis, also commented on the rarity of the Jarisch-Herxheimer reaction in cardiovascular syphilis, in contrast with early syphilis and central nervous system syphilis.

Encouraged by the relatively lessened reaction tendency of penicillin G over the more crude product, the University of Pennsylvania group in May, 1949[17], reported the results of the treatment of 50 cases of cardiovascular syphilis with penicillin therapy alone, without preparation; of 12 patients with cardiovascular syphilis and congestive failure, in whom penicillin and methods to combat congestive failure were used simultaneously. In this group not only were untoward effects lacking, but the distinct impression prevailed that these patients responded better than most patients with cardiovascular syphilis and decompensation who were treated, as was often the case in the pre-penicillin era, with measures aimed only toward combating congestive failure. Experience with these two groups of cases led to the belief that therapeutic shock in cardiovascular syphilis treated with penicillin is indeed uncommon; and that therapeutic paradox, if it occurs, is a rarity. Various hypotheses including that of a toxic action of arsenicals upon already diseased tissues, rather than a wholesale sudden liberation of toxic spirochetal disintegration products were discussed to explain therapeutic shock. If therapeutic paradox occurs, they do not believe it is common or that it is caused by too rapid cure with disturbance of function with resultant rapid fibrosis.

Subsequently[19] this group reported observations on 111 penicillin-treated cardiovascular syphilitic patients (simple aortitis, 48 cases; aortic regurgitation, 51 cases; aortic regurgitation and aneurysm, 9 cases; and aneurysm, 3 cases) with reemphasis of the virtual absence of significant therapeutic shock and paradox.

Serologic Effects of Penicillin Therapy in Cardiovascular Syphilis. The serologic effects of penicillin therapy on cardiovascular syphilis are bound to be diasappointing. The frequent association of neurosyphilis with syphilitic cardiovascular involvement (for example, 45.2% of the 111 University of Pennsylvania patients also had central nervous system syphilis) may account for much of the poor serologic effect of treatment. The University of Pennsylvania group[19] (March, 1951), found, disregarding the 6 cases without follow-up, there were 85 cases (80.9%) positive before treatment, and 86 cases (81.9%) positive after therapy. Twenty cases (19.1%) were negative before treatment, and 19 cases (18.1%) were negative after treatment. Although 7 of the cases with a positive serologic reaction yielded negative reactions following treatment, 8 of the original 20 cases that had negative reactions prior to treatment had positive serologic status after penicillin therapy. Thirty-six cases (42.3%) of the 85 patients with positive results in their tests showed a drop of 2 or more tubes in the quantitative test. Thirty-seven (43.5%) of the 85 cases showed no change in the quantitative tests. Coale and his group[8] had similar poor serologic results, while Weir *et al.*[62] and Johnson and Shapiro[32] found a post-penicillin therapy drop in serologic titer in their relatively small series of cases. Three of Leech's[36] 17 patients developed negative reactions

to the Wasserman or Hinton tests after treatment.

Clinical Effects of Penicillin Treatment of Cardiovascular Syphilis. Assuming that all the deficiencies previously mentioned as inherent in the determination of the effect of penicillin therapy of cardiovascular syphilis are corrected, one could not make definite statements regarding the clinical effectiveness of such treatment because the period of observation is as yet rather short. Up to 1951, 1243 days was about the longest period that reported patients have been observed[32]. However deficient the data are, some of the information available on this aspect of the problem are worth mentioning. Coale and his co-workers[8], for example, noted no striking results, but the overall picture was good. Flaum and Thomas[24] 1949 stated that 7 of their patients with aortic insufficiency, "claimed to be improved after treatment". This apparent improvement could be due to a general systemic improvement following the eradication of the chronic low-grade syphilitic infection. Leech[36] reported that all but 2 of his patients were improved or unchanged. Death in 3 was not attributable to treatment. Chapman and Morgan[7] observed relief of pain in patients with aneurysm, but their treatment schedule included potassium iodide and bismuth simultaneously. Wheeler and Curtis[63] also reported improvement in symptoms, but there were 2 possible therapeutic paradoxes. In one of Johnson and Shapiro's[32] cases, there were significant orthodiagraphic and roentgenographic changes indicating enlargement of an aneurysm. The patient died of tracheal obstruction 2 days after completion of treatment. Five patients died 2, 270, 350, 527, and 854 days, respectively, post-treatment. Most of the patients experienced weight gain and a feeling of well-being. Weir, Roberts and Tullis[62] in a preliminary comparison of the post-treatment with the pretreatment status of their patients indicated that although a few patients were graded as "worse" in the post-treatment period, it is felt that in no case was deterioration hastened by penicillin therapy. The University of Pennsylvania group[19] found that "penicillin is admirably tolerated by the decompensated heart, with clinical improvement in a high proportion of cases. Anginal pain was relieved without recognizable shock or paradox in 4 out of 5 cases. In syphilitic aortitis 'uncomplicated', observed for from 3 to 58 months, one-third are improved, one-half unchanged and only one-sixth were worse (one death of bronchopneumonia). In aortitis with regurgitation 64% are improved, 20% unchanged and 16% are worse. In aneurysm with regurgitation the number is too small for analysis, but 4 or 5 kept under observation improved. Of 3 large saccular aneurysms, one lapsed from observation, one died in a wiring operation, and one was unchanged."

Electrocardiographic Changes Following Penicillin Therapy. In this phase of the subject of penicillin therapy of cardiovascular syphilis, it is necessary to differentiate the electrocardiographic effects induced by penicillin *per se* and those incident to the changes in cardiovascular status this therapeutic agent induces. Steiger and Edeiken[54b] in their studies on the electrocardiographic changes before, during and after penicillin treatment in early syphilis, found alterations in 42.5% in a second series of 40 cases. In an earlier report (1947[54a]), they had found 50% incidence among 30 cases, or an aggregate of 45.7% of 70 cases. The electrocardiographic changes which were T-wave, and in some cases RS-T sequent changes in limb or chest leads,

or both, occur in all phases of early syphilis. Penicillin does not seem to be responsible for these changes. The changes are usually transient, but may also remain permanently. Binder and his group[2] encountered transient T-wave inversion in 3 patients who developed severe reactions during penicillin treatment. They resemble changes observed in other allergic reactions. With respect to the electrocardiographic changes produced by penicillin in the treatment of cardiovascular syphilis, there are only scattered data, the exact significance of which is not clear. Edeiken and his group[17], in 1949 stated that although a large percentage (50%) of their cases showed electrocardiographic abnormalities either before, during or after penicillin treatment, one cannot conclude that they are all directly or solely due to the syphilitic infection. Significant T-wave changes were noted during the course of treatment in 8 patients. Moore[39] observed that tracings taken during course of treatment did not indicate that penicillin irritated the heart, and in several instances improvement was seen. Peralta and Castenada[46] noted that 7.8% of their patients had altered electrocardiographs. Coale and his colleagues[8] concluded that nothing definite could be concluded by following the electrocardiograms. Johnson and Shapiro[32] observed that "the electrocardiographic tracings, except for changes which go with left ventricular strain due to aortic insufficiency or changes due to coronary involvement, showed no pattern which could be considered pathognomonic of cardiovascular syphilis."

Summary Statement and Proposed Therapeutic Regimen. The problems of penicillin therapy of cardiovascular syphilis may at this time be summarized by employing the questions asked by Edeiken, Ford and Stokes[19] regarding this subject. We emphasize again the relatively subjective character of the available information.

1. "Can penicillin therapy be given safely to patients with cardiovascular syphilis?" Penicillin is relatively free from severe reaction.

2. "How common is therapeutic shock and therapeutic paradox in penicillin-treated cardiovascular syphilis?" Relatively few unequivocal reactions have been observed, and the University of Pennsylvania group observed no serious examples in 111 cases. The factor of coincident neurosyphilis in producing febrile "Herxheimer" reactions is reemphasized.

3. "Are there any contraindications to the use of penicillin in cardiovascular syphilis?" Patients exhibiting a variety of processes, previously contraindicating arsenical therapy, have been given penicillin treatment without serious untoward effects.

4. "Does penicillin stop the progress of cardiovascular syphilis?" There is evidence to suggest that the course of the disease is favorably influenced by penicillin, but no definite statement can be made before a long follow-up period, at least 10 years, has elapsed, and a large number of cases have been studied clinically and pathologically.

5. "What effect has treatment on the serologic test for syphilis?" The information on this point indicates that little may be expected from treatment in the way of serologic reversal. The coincidence of neurosyphilis with the cardiovascular process plays a large role in this lack of serologic reversal.

6. "Should patients with suggestive, but not positive, signs of aortitis be treated with penicillin?" We agree with Edeiken, Ford and Stokes in saying yes to this question. In view of the uncertainties of diagnosis of uncomplicated syphilitic aortitis and the

safe and probable effectiveness of penicillin therapy, the patient should be given the benefit of the doubt, not only because it is practically without danger; but it is inexpensive and not time consuming. In the past many patients were not treated because even presumptive diagnosis condemned them to prolonged, costly and even dangerous therapeutic regimen.

To these may be added:

7. Is treatment with bismuth and iodides necessary prior to penicillin therapy of cardiovascular syphilis? Although, according to Willcox[67] most British physicians are employing such preparatory treatment, it is obvious from the data presented above that this seems unnecessary from the reaction standpoint, at least. Whether the eventual outcome of treatment will be better with combined therapy or penicillin alone is still unanswered.

Assuming, from the data presented, that penicillin therapy is the safest agent yet produced for cardiovascular syphilis, we suggest that the treatment scheme of the University of Pennsylvania group[19] be employed until a more convenient or effective regimen is evolved. "The advocated treatment includes hospitalization, two-hour schedule, crystalline penicillin G (4,800,000 to 9,600,000 units in 40,000 to 80,000 unit individual doses), but procaine penicillin may be given to hospitalized patients on a 600,000 unit single, or 300,000 unit two-injection daily schedule for equal total dosage. The ambulatory use of this salt is under investigation. By present standards, repetition of courses in excess of two of 9,000,000 units seems unnecessary. . . . The concomitant or subsequent use of heavy metal was not studied in this series, but seems on general experimental grounds to be unnecessary."

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OTO-RHINO-LARYNGOLOGY

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TRACHEOTOMY IN BULBAR POLIOMYELITIS: A REVIEW

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DEATH in acute anterior poliomyelitis results almost solely from bulbar and bulbo-spinal involvement. Among other effects, this involvement causes respiratory embarrassment and failure, due to paralysis of the muscles concerned in swallowing, breathing, and coughing. Inability to swallow results in pooling of salivary secretions which can block the larynx and be aspirated; loss of the ability to cough can lead to atelectasis and "drowning in one's own secretions."

These contingencies were dealt with by postural drainage, as suggested by Durand[11] in 1929, continuous mechanical aspiration of pharyngeal secretions, parenteral instead of oral or gavage feeding, administration of oxygen by catheter or mask, occasional bronchoscopic aspiration when indicated, and, when there was sufficient paralysis of the diaphragm and the intercostal muscles to warrant it, the use of the respirator. When death occurred in spite of these measures, it was usually ascribed to progressive involvement of the respiratory and circulatory centers of the brain stem. To this eventuality the physician had become reconciled, since he felt powerless to prevent or control the spread of this infection.

The use of tracheotomy in the treatment of bulbar poliomyelitis was first reported by Wilson[41], from Boston, in 1932. Other reports[10,13,18,27,42,43] describing and advising the occasional emergency use of tracheotomy in selected cases of acute bulbar poliomyelitis appeared sporadically during the next 15 years.

In 1946, compelled to cope with a severe epidemic of poliomyelitis, including 400 bulbar cases, the Minneapolis group performed 75 tracheotomies. The reports[2,8,21,30,32] of their experiences in these cases and their advocacy of early operation gave great impetus to the use of tracheotomy in bulbar poliomyelitis. This was reflected in a succession of articles[7,15,17,22,24,25,34,37,40] describing an increasing use of tracheotomy, not only as a life-saving measure in respiratory emergencies, but also as a prophylactic procedure to prevent hypoxia, hypercapnea, atelectasis and pneumonia, and pulmonary edema. This advocacy of the use of tracheotomy based on greatly liberalized indications, including so-called "prophylactic" tracheotomies, has met with strong disapproval from a number of workers[5,36]. Curiously, this seems to have developed into a sort of sectional issue (except for occasional dissenters within both regions). In the Midwest and West they favor more frequent and earlier trache-

otomy, which is considered to be life-saving; on the other hand, in the East, where tracheotomy was first performed, most are wary about these liberalized indications and sudden 'enthusiasm' for this operation, maintaining that the great majority of bulbar patients can be saved by expert management, without tracheotomy.

It will be the aim of this paper to review the facts relating to both sides of this controversy and attempt to deduce areas of reconciliation which may be useful in the care of these desperately sick patients. A general discussion of the technique of tracheotomy and the post-operative care, as modified by the use of the respirator and the unique conditions that obtain in poliomyelitis, will be outlined.

Clinical Pathology and Pathological Physiology. Acute bulbar poliomyelitis presents disastrous derangements of at least 4 functions, namely: 1) swallowing, 2) breathing and coughing, 3) circulation, and 4) cerebral; one or more of these can occur in the same patient.

To aid in understanding the symptoms of this affection, bulbar polio cases can be grouped anatomically as follows: 1) Cranial Nerve Nuclei Group; with impairment of the swallowing mechanism and laryngeal function; 2) Respiratory Center Group; 3) Circulatory Center Group; 4) Bulbo-Encephalitic Group, and 5) Bulbo-Spinal Group, with paresis of the respiratory muscles.

A brief discussion of these groups will be of value.

1) With involvement of the cranial nerve nuclei, the significant symptoms result from impairment of a) the swallowing mechanism and b) laryngeal function. a) Starting with nasal speech and nasal regurgitation, progression of pharyngeal paresis results in pooling of secretions in the pharynx; if severe, this can lead to obstruction of the larynx, reflex laryngeal spasm, aspiration of saliva and food, atelectasis and aspiration pneumonia, and finally to "drowning in one's own secretions."

b) Since destruction of the cells of the nucleus ambiguus (the motor nucleus which governs abduction and adduction) varies, the position of the paralyzed vocal cords likewise varies. When there is paralysis of both abductors (rarely), the cords may be almost touching in the midline on inspiration, and blown apart on expiration. At best, this would cause controlled, shallow respirations; at worst, sudden asphyxia. Paralysis of both adductor muscles impairs speech and prevents efficient coughing. With only one side affected, these functions would be impaired to a lesser degree. Rarely, anesthesia of the larynx occurs.

When there is any severe type of laryngeal involvement, the aspiration of secretions or food is obviously extremely dangerous. (There is no question regarding the need for tracheotomy in such a situation.)

In passing, it should be remembered that the act of coughing can be impaired, even though laryngeal function is intact, if there is severe paralysis of the diaphragm and the intercostal muscles. Briefly, the act of coughing consists of 1) inspiration, 2) closure of the glottis, 3) increase in intrathoracic pressure, 4) opening of the glottis, and 5) sudden expiration with release of the increased intrathoracic pressure. To obtain an effective cough, it has been estimated[3] that the positive intrathoracic pressure may rise to 40 mm. of mercury. Since the positive pressure in the respirator is rarely over 5 mm. of mercury, this would be insufficient by itself to produce an effective cough. A lack of coordination of the muscles involved in this complex cycle, due to central disturbance, could

also impair the cough reflex.

2) Involvement of the respiratory center, due to destruction of the ventral portion of the reticular substance of the medulla (Brown *et al.*[8]) at first causes a variation in the rate and the depth of inspiration, together with the usual symptoms of hypoxia, namely, anxiety, restlessness, increased pulse rate and rise of blood pressure, with or without cyanosis. Increasing damage to the center results in longer periods of apnea and respiration of the Cheyne-Stokes type; with this come increasing restlessness, cyanosis, confusion, delirium and coma. (Sedatives should be used with extreme caution, because of possible further depression of the respiratory center.) Intensive oxygenation by whatever means deemed advisable in the particular case is essential.

The importance of adequate oxygenation is illustrated by a case cited by McIntosh and McLeay[22]. The patient had severe bulbar poliomyelitis and encephalitis; both vital centers were involved and voluntary respiration ceased for 12 hours. During this time he was maintained in a respirator after a tracheotomy had been performed. Then gasping respirations began and breathing gradually returned to normal. His circulatory center, less involved, also recovered.

3) Damage to the circulatory center is manifested by an irregular, thready and rapid pulse (140 to 200) out of proportion to the fever. The blood pressure varies and the pulse pressure is markedly reduced. The patient appears dusky red, is anxious and restless. With increasing failure the blood pressure drops further, the pulse becomes impalpable, and the skin is cold, clammy, cyanotic; delirium, coma and death follow. It is imperative that intensive oxygen therapy be instituted in an attempt to tide the patient over the acute inflammatory period. (Sjoberg[34] advises that the blood pressure be taken constantly, because it seems to be a sensitive indication of hypoxia. When the blood pressure rises to 170 to 200, the patient becomes ashen gray, slightly cyanotic, and is in a cold sweat.)

4) Encephalitic symptoms are anxiety, restlessness, tremors and twitchings, irritability, confusion, lethargy, coma and, particularly in children, convulsions.

It should be noted here, as stressed by Galloway[15,16], Brown, *et al.*[2,8], and others, that these symptoms and the symptoms resulting from failure of the respiratory and circulatory centers, can also be caused by cerebral hypoxia and anoxia, due to partial obstruction of the airway, inadequate function of the muscles of respiration, and pulmonary atelectasis and edema. Pulmonary acidosis from too much retained CO_2 can produce a similar picture. It is only when the symptoms of cerebral irritation and damage persist after adequate oxygenation is assured and hypercapnea is eliminated as a cause, that they should be ascribed to viral involvement of the encephalon and the medullary centers.

As an example of this, Galloway[13] describes a case in which a patient with poliomyelitis had progressed from confusion and disorientation to complete coma. The first impression was that the symptoms were due to viral involvement of the brain. A direct laryngoscopy showed that the pharynx, larynx and trachea were filled with secretion. Aspiration gave temporary relief. Eventually respiration ceased completely for 3 minutes while a tracheotomy was done. Secretions were aspirated and artificial respiration was given until the patient could be placed in a respirator. In 45 minutes he was

conscious and in 2 hours nearly normal mentally.

5) When, in addition to bulbar damage, there is severe spinal cord involvement with paralysis of the diaphragm and the intercostal muscles necessitating the use of a respirator, it is essential that a clear airway be present. Inspiration forced by the respirator against a partially obstructed airway creates a negative pressure which sucks fluid from the pulmonary capillaries into the alveoli and produces pulmonary edema. In such a contingency oxygen under positive pressure, by mask or preferably by tracheotomy tube, should be administered. As noted above, in these cases with severe paralysis of the respiratory muscles, cough is often impaired, so that the patient cannot expel tracheobronchial secretions effectively. Bronchoscopic aspiration, with or without tracheotomy, may be required to prevent or relieve atelectasis.

Sjoberg's Angle Sign. Although it should logically be discussed under the "Cranial Nerve Nuclei Group," it has seemed to me that it would be less confusing to place it here. According to Sjoberg [34], "the angle sign seems to be caused by paralysis of the anterior neck muscles as well as of the pharyngeal constrictors. There results a contracture or tonus excess in the antagonists, that is, in the remaining, non-paralyzed muscles, which normally maintain the larynx in position. Such muscles are: the mylohyoideus . . . the digastricus . . . and the stylohyoideus. The result is that the larynx is pulled upward and backward, thus blocking the air passage to the trachea. Therefore, the epiglottis does not fall back, but the opening of the larynx is pushed or pulled up under the base of the tongue, whereby the patient is suffocated. . . . In certain cases, one can see that the point of the angle is so sharp that a transverse skin fold, which divides the bottom of the chin from the neck, is extremely deepened. The neck appears as if cut off from the bottom of the chin by a string, . . . as though a noose had been placed around the neck and pulled tight. In the depth of this fold one can palpate the hyoid bone. . . . The patients are literally strangled or hanged by those remaining muscles which are not paralyzed and which pull the hyoid bone upward and backward. . . . This is a warning signal from the patient himself that danger is imminent. He may suffocate . . . if a tracheotomy is not performed immediately . . .".

Biochemical Changes. Since a principal problem in this disease is the prevention or correction of hypoxia and hypercapnea, a brief discussion of these changes follows.

Anoxia. Galloway[14], citing animal experiments by Windle and Becker[46], and Morrison[26], asserts that grave and lasting effects result from periods of anoxia as short as 3 to 5 minutes. According to Courville[9], irreversible changes occur after 3 to 8 minutes of anoxia. Among the sequelae of oxygen deprivation he lists twitchings, convulsions, even decerebrate rigidity, and psychic aberrations. Thorner and Lewy[38] believe that a single period of anoxia of 60 seconds' duration leaves evidence of morphologic changes. Mental symptoms of hypoxia occur early; these are depression, confusion, disorientation, irritability, unresponsiveness, lethargy and coma. Antagonism and combativeness often occur. Galloway[14] stresses the narrow margin between oxygen want and disaster. He emphasizes that cyanosis may be a late symptom or may be missed at night. Restlessness is an important early symptom because it denotes increased oxygen need and the unwary are tempted to give sedatives which may be fatal.

The effectiveness of oxygenation can be followed by the use of the Milliken oximeter and checked by determinations of arterial oxygen. This instrument determines the relative concentration of oxyhemoglobin to reduced hemoglobin by means of a photoelectric cell. It is possible to detect a fall in arterial oxygen before the patient feels fatigued and before clinical signs of hypoxia appear and it helps determine the effectiveness of mechanical artificial respiration. By its use one can determine how long a patient can be left out of the respirator.

The concentration of oxygen used should ordinarily not exceed 60%. In emergencies it may be necessary to use 100% for a limited time. Oxygen under pressure of about 5 cm. of water increases the exchange of the gas at the alveoli. This positive pressure also assists in combating pulmonary edema. (If the chest excursions are not strong enough to produce expiration against positive pressure oxygen, a mechanical respirator is required, unless a Bennett flow-sensitive positive pressure unit is available.)

Hypercapnea. The oximeter gives no indication of the co-existent state of acidosis. The effect of anoxia upon the heart is apparently not so great as that of excess carbon dioxide. According to Seevers[33], hypercapnea first causes an increased heart rate, later disturbances of rhythm.

Blalock, Harrison and Wilson[4] demonstrated that carbon dioxide can reach dangerous levels in the arterial blood, even while oxygen saturation is still normal. For this reason the oximeter cannot be relied upon in place of close clinical observation, and oxygen administration alone is not enough; a clear airway for elimination of carbon dioxide is essential. According to Stimson[36], a climbing venous plasma carbon dioxide combining power above a normal or 62 volumes per 100 cc. is a good indication of the need for better ventilation. A decrease in the pH of the urine is also significant. Gamble[35] cautions that respiratory acidosis gives opposite blood findings from those of metabolic acidosis and must be interpreted in the light of blood pH and compensatory mechanisms. The tests must be done on arterial or capillary blood.

In patients who receive enough oxygen, but who fail to synchronize their respiratory movements with those of the respirator and, which curare (or electrophrenic stimulation) does not correct, the cause in many instances is overstimulation of the respiratory center by the presence of excessive CO_2 and not involvement of the center itself. When the pulmonary acidosis is corrected, the majority of these patients synchronize with the respirator movements very rapidly.

Bower and his associates[7] state, "Acutely ill patients placed in respirators were found to be in profound states of respiratory acidosis with systemic attempts at compensation. Such states if not rapidly corrected, were soon fatal. This acidosis proved to be due to insufficient eradication of CO_2 and occurred despite the offering of additional oxygen. This inadequate gaseous exchange and building up of CO_2 in the lungs was due principally to pooling of secretions in the upper airway, but when this was overcome by the liberal use of tracheotomy, other major contributory causes became apparent, among which were plugs of mucus occluding bronchi, atelectasis, inadequate removal of excessive and retained secretions due to insufficient or improper aspiration or failure to bronchoscope a patient when indicated, pulmonary edema, pneumonia or pneumothorax. Regardless of cause,

pulmonary acidosis ends in death, unless relieved."

Potassium Deficiency. This can arise from excessive loss of saliva, acidosis and cell destruction and cause cardiac muscle weakness. Potassium may be given safely intravenously, only if checked with careful blood studies. It can be given more safely subcutaneously in Darrow's solution. It is safest when given by mouth. Therefore, feeding by gavage should be started as soon as feasible.

Indications for "Early" Tracheotomy. Those workers who advocate the performance of early tracheotomy maintain that tracheotomy has too often been looked upon as a measure of last resort and effects have been attributed to it which were due to the serious condition for which it was done, or to the fact that intervention came too late. They assert that to prevent anoxia is better than having to correct it after permitting it to happen, since damaged nervous tissue is particularly susceptible to oxygen lack and this damage is usually irreversible. If tracheotomy can avoid even one period of severe anoxia in these cases, it would be worth while, since the margin between life and death in these patients is so narrow that one such episode may kill them. This group of workers feel that early elective tracheotomy performed before respiratory obstruction and anoxia can occur is the ideal treatment and in selected cases it is a life-saving measure. They admit that a number of these tracheotomies may be needless, but argue that the danger of waiting is much greater than that of operating.

If the patient has not improved on properly applied postural drainage, aspiration and administration of oxygen and fluids, if he is increasingly restless, disoriented and exhausted, they maintain that a tracheotomy should be done at once rather than wait for a failing heart, marked cyanosis or coma, because by then irreversible changes may have taken place. The appearance of laryngeal stridor, dyspnea despite adequate chest excursions, cyanosis and severe encephalitic symptoms indicates serious obstruction of the airway and requires an immediate tracheotomy. In a desperately ill patient they consider it more dangerous to delay a tracheotomy than to perform it. They feel that a tracheotomy is essential in many of these patients who are put in a respirator because the mechanical respiratory excursions will produce severe pulmonary edema if there is any obstruction to the airway. Some workers assert that in patients unable to swallow, a tracheotomy is required as soon as secretions accumulate in the oral pharynx. Miller and Buck[24] maintain that secretional obstruction of the respiratory tract is the outstanding indication for tracheotomy, rather than paralysis of the vocal cords which is a rare complication. Another indication advocated by Sjoberg[34] is the appearance of the "angle or rope dent" sign described above, which is indicative of imminent asphyxia. It is stressed that the patient should not be allowed to sink into coma because of the fatalistic attitude that the condition is due to the virus infection, since the symptoms of anoxia can simulate those due to a severe infection. Strobel and Canfield[37] state that indications for tracheotomy are not always obvious. A patient with an apparently mild paralysis may have severe respiratory difficulty in an alarmingly short time, while a patient with bulbar signs that seem to be rapidly progressing may recover almost completely over night.

In these cases the importance of tracheotomy is that it accomplishes a by-pass allowing air to enter the trachea without being sucked through the pharynx, thus preventing secretion

from being drawn into the lower airway. Other advantages of tracheotomy are easy removal of mucus and secretion from the respiratory tract, ability to bronchoscope the patient through the tracheotomy opening without requiring his cooperation for the emergency removal of mucous plugs, either when in or out of the respirator, easier maintenance of adequate oxygen tension, and in facilitating the treatment of pulmonary edema by applying positive pressure.

A composite view of the indications for early, elective tracheotomy advocated by these workers (Galloway[13,15], Seifert[16], Priest[30,32], Goltz[30,32], Boies[30], Bower[7], West[40], Brown[8], Baker[2], McIntosh[22], McLeay[22], McLorinan[23], Grulee and Panos[19], Sjoberg[34], Miller and Buck[24], Mitchell and Hill[25], Peterson and Ward[28], Younger and Koller[31], Strobel and Canfield[37], and others) is now outlined. They advise tracheotomy:

1) When, in spite of proper postural drainage and continuous pharyngeal aspiration, it is impossible to prevent pooling of secretions in the pharynx, resulting in spill-over into the airway, with laryngeal stridor, rales in the chest, respiratory distress and recurrent cyanosis; in short, when there is progressive hypoxia accompanied by the presence of secretions in the pharynx.

2) With stupor or irrationality sufficient to make the patient oblivious to the accumulation of secretions in his airway, particularly if he is in a respirator.

3) If there is fluid accumulation and the patient later requires a respirator.

4) In the presence of excitement and unmanageability, causing the patient to resist pharyngeal aspiration strenuously.

5) If there is unconsciousness or pronounced restlessness in a patient who does not respond to other treatment in a few minutes.

6) If there is pronounced restlessness (which often means air hunger) or stupor in a patient in a respirator, even if paralysis is apparently only of the spinal type.

7) When there is clinical or Roentgen-ray evidence of atelectasis, pneumonia, or pulmonary edema due to secretion in the lower airway.

8) In the presence of rapidly progressive bulbar symptoms.

9) In the presence of grave signs of vasomotor or respiratory center failure.

10) When there is inability to cough effectively, especially if the patient is in a respirator.

11) When there is bilateral paralysis or spasm of the vocal cords.

12) On the appearance of the "angle or rope dent" sign (Sjoberg[34]).

13) If the attendants are untrained or inefficient and the equipment is inadequate.

Galloway feels that lack of cooperation is more often a sign of anoxia than a matter of temperament. In doubtful cases he maintains that it is safer to perform a tracheotomy than to wait and, therefore, the operation should be performed more often, not less often, when the attending team has had little experience with the disease.

Seifert[16] stated: "I have seen and taken care of patients with poliomyelitis for 18 years. Patients with bulbar poliomyelitis of the same type that we have seen in the last two and a half years have died under my care before this. It took a supervising nurse and a laryngologist to teach me that there was something to do about bulbar poliomyelitis."

Sjoberg[34] asks us to remember, ". . . that the condition of these patients whose lives have now been saved, was before considered quite hopeless, and

they invariably died of suffocation. . . . So far, thanks to tracheotomy, 12 of 14 patients whose condition was considered hopeless up to now, have been saved."

Mitchell and Hill[25] are convinced that tracheotomy in addition to other measures can save the lives of some bulbar poliomyelitis patients that would otherwise die. Their 1949 mortality rate was only 10.2% (of 39 bulbar poliomyelitis patients, 10 were subjected to tracheotomy; of these, 4 died). In 1946 the mortality rate in their bulbar poliomyelitis patients was 33.3%; in 1948 it was 39%.

Miller and Buck[24] reviewed 388 cases of bulbar poliomyelitis in the 1948 epidemic in Los Angeles. Of these, 198 (51.0%) had a tracheotomy. The total mortality rate in the group was 28.8%; the mortality rate of the tracheotomized patients was 38.8%. They are convinced that many would have died of anoxia, atelectasis, pulmonary edema or pneumonia if tracheotomy had not been done, and they feel that early tracheotomy cannot be overstressed in the management of acute bulbar poliomyelitis. They assert that tracheotomy saved at least half of the patients of a type who previously died.

The Arguments Against Early, Prophylactic Tracheotomy. In general, workers in the East maintain that tracheotomy is seldom necessary if the patient is given expert management and care.

Wilson[41-43] stated that tracheotomy is a radical step, often life-saving and often dramatically effective. However, he felt that it is necessary only in a small fraction of the cases of bulbar poliomyelitis. Several other workers (Stimson[36], Shaw, Pierce and Anderson, Boines[5], Elkins[12], Hoyne[20], Wesselhoeft[39], and others) have seldom seen any indication for tracheotomy.

Elkins[12], writing from the Mayo Clinic, stated that tracheotomy has been indicated in only a few cases.

Boines[5] states that the only true physiological indication for tracheotomy is paralysis of the larynx and vocal cords. The accumulation of oral secretions in the pharynx is not an indication because this condition can be managed successfully with experienced medical and nursing personnel. In the absence of experienced personnel, the necessity for tracheotomy must be decided upon as the emergency arises. He cites his experience with 67 cases of bulbar poliomyelitis, treated in the Doris Memorial Contagious Unit of the Wilmington General Hospital. Thirteen, (20%), died due to involvement of the respiratory center. Of the remaining 54 cases, 26 had severe involvement with complications, but recovered without the use of tracheotomy or respirator; the remaining had moderate involvement and recovered.

Stimson[36] cites the following indications for tracheotomy in poliomyelitis: 1) Bilateral abductor paralysis of the vocal cords. This causes a mechanical obstruction which must be bypassed. 2) Inability to keep the airway reasonably clear. Some clinics with good teamwork can be notably more successful in this than others that are overcrowded or have inadequate and untrained personnel. 3) Progressive hypoxia, not otherwise correctible. He states that the following conditions which have been cited as indications for tracheotomy are insufficient indications. 1) Inability to cough. 2) Inability to swallow. 3) Any laryngeal involvement besides bilateral abductor paralysis. 4) Pulmonary edema. This requires positive pressure artificial respiration, but besides through a tracheotomy tube, this can be given by mask or by a hood on a respirator. 5) Atelectasis. This, he believes, requires im-

mediate suction which can be better done visually by means of bronchoscopy, than by blind suction through a tracheotomy tube.

Stimson[36] collected the figures of 6 hospitals from Detroit to Boston totaling 1751 cases of poliomyelitis admitted in 1949; among these were 311 bulbar and bulbospinal cases. Comparing the statistics from the 6 hospitals with the statistics in the Los Angeles epidemic of 1947, he states that of 603 bulbar poliomyelitis patients in Los Angeles, 354 were subjected to tracheotomy; of the 311 bulbar cases in the Eastern hospitals, only 19 were so treated. Thus more than 50% of the bulbar patients had tracheotomies in Los Angeles compared with only 6% in the Eastern hospitals; in other words, more than 1 out of every 10 patients admitted with poliomyelitis had a tracheotomy in Los Angeles, but only 1 in about 100 had a tracheotomy in the Eastern hospitals. The mortality rate of the bulbar cases in Los Angeles was 19.4%, with an overall mortality rate of 4.1%; the mortality rate of the bulbar polio cases in the Eastern hospitals was 15.7%, with an overall mortality rate of 3.2%.

(It should be noted, however, that further statistics from the Los Angeles County Hospital show that in 1949, there were 1128 cases of poliomyelitis admitted to the hospital. Of these 105 were tracheotomized, roughly 1 out of 10. There were 22 deaths; a general mortality rate of only 1.95%. This is an example of the danger of comparing statistics where similar conditions do not prevail.)

Stimson[36] states that Van Riper, the Medical Director of the National Foundation for Infantile Paralysis, noted in 1949 that there was generally a markedly lessened tendency to do tracheotomies from that which he had observed in the preceding years."

In general the disadvantages of tracheotomy are cited as follows:

1.) The bulbar poliomyelitis patient is already weak when the ordeal of tracheotomy is added; the patient needs rest and a minimum of handling; the loss of the power of speech adds to the apprehensiveness.

2.) Special equipment and nursing care are needed for the administration of humidified air, oxygen and for aspirating.

3.) Children must be kept well restrained to prevent them from pulling out the tube.

4.) Tracheotomy delays the return of swallowing by 2 weeks or longer.

5.) The tracheotomy tube narrows the airway and acts as a foreign body to increase tracheal secretions. There is frequent crust formation which causes obstruction.

6.) Constant experienced nursing care around the clock is necessary in order to avoid sudden suffocation due to obstruction of the tube, since the patient cannot call for help. Suction of the pharynx must still be continued to prevent saliva from entering the airway.

7.) The constant suctioning of the trachea by the catheter causes inflammation, trauma and secondary infection. Repeated bronchoscopy may be necessary through the tracheotomy opening due to crust formation.

8.) Complications of tracheotomy may be pneumothorax and mediastinal emphysema; in respirator cases there may be prolonged post-operative bleeding from the wound.

9.) Delayed healing of the tracheotomy wound and stenosis of the trachea can occur.

10.) There is always a certain amount of surgical risk.

Boines[5] states that there is no question that tracheotomy performed where obstruction of the airway cannot be relieved by other methods is

life-saving. However, he feels that good medical and nursing care by specially trained personnel will save more lives in bulbar poliomyelitis than any surgical procedures.

Areas of Reconciliation. The preponderance of opinions in American and foreign literature favors the performance of early, elective tracheotomy as a life-saving measure. However, one should not be swayed by mere numbers, because it is only natural that workers performing tracheotomy (or any other procedure that is relatively new) will be inclined to write about it, whereas those who are relying upon older less dramatic methods will be less apt to "break into print" for the sake of denying the need for tracheotomy. When we compare the statistics from Los Angeles, where one out of every 2 bulbar polio patients was tracheotomized, with the reports from Eastern hospitals (see Stimson[36]) where only one in 20 was tracheotomized, a ratio of about 10 to 1, we realize what a wide gulf separates the two schools of thought. Heartwarming reports of dramatic and even miraculous recoveries following emergency tracheotomy in individual cases tend to pale when mass figures of comparative mortality rates from different sections of the country are placed under the cold light of statistical analysis. On the other hand, individual workers attest both by their clinical experience and a comparison of their own mortality rates, before and after the use of tracheotomy, the unquestionable value of early operation. However, the undisputed wisdom of performing tracheotomy in certain selected cases does not necessarily apply to the many others that have been performed "prophylactically".

During the last 20 years, with the general improvement in the technique of tracheotomy and especially with the greatly improved after-care, surgical morbidity and mortality have been greatly decreased, so that there has been a general tendency to perform the operation earlier and more often.

All agree that hypoxia and hypercapnea are constant threats which must be combatted by all possible means and in selected cases tracheotomy is unquestionably a very effective means. The crux of the problem is to decide which patient will probably live without tracheotomy and which will probably die unless a tracheotomy is done. All the indications previously outlined require experienced evaluation in each individual case, and these patients have to be under constant observation by carefully trained personnel, so that crucial decisions be made at the proper time. For example, a patient with an apparently mild paralysis may develop severe respiratory difficulty in a very short time, while a patient with bulbar signs that appear to be progressing rapidly may recover almost completely over night.

There is no question that a tracheotomy should be performed in those cases where there is a clear indication of respiratory obstruction which can not be rectified by any other means at the command of the attending physicians. Also, in those cases where a patient seems desperately ill and tracheotomy seems a very dangerous procedure, experience has shown that the patient should be given the benefit of the doubt and the operation performed, in spite of the understandable reluctance on the part of the surgeon. The charge by some workers that the operation is mutilating seems trivial: of what moment are esthetic considerations in a matter of life and death? Furthermore, if a tracheotomy is properly performed and the post-operative care is excellent, I have never felt that

the operation *per se* is particularly harmful. In these cases, if some avoidable tracheotomies are performed, I feel certain that they will not alter the vital statistics. Therefore, in those institutions where expert care is constantly available, the performance of a tracheotomy will not enhance the danger, but on the other hand, may prevent the occurrence of sudden anoxia in a small number of cases.

It has been stated that tracheotomy is more necessary when the attending team has had meager experience with the disease; that if all personnel were thoroughly trained and the mechanical arrangements perfect, tracheotomy might seldom be required, but that unforeseen failures occur too easily. As an example, Galloway[15,16] cites an instance where an assistant substituted a fine medicine dropper tube for a proper glass connecting tube and thus prevented proper aspiration which made an emergency tracheotomy necessary. He tells of another patient who received improper aspiration for 2 half-hour periods resulting in anoxia and a decerebrate state. However, this does not strike me as a valid reason for early, prophylactic operation, because poor post-tracheotomy care can lead to respiratory obstruction with the same dire results. It is difficult for me to see, in the light of my past experience with the general caliber of post-tracheotomy care, why there would be any likelihood of improved care of a tracheotomized bulbar patient by the same type of untrained and incompetent personnel as existed prior to the tracheotomy. Certainly the lack of training and unfamiliarity would not cease abruptly merely with the performance of a miraculous tracheotomy; as a matter of fact tracheotomy might even complicate the treatment in such a situation. Where neither the equipment nor the personnel is adequate, then it would seem to me that the early, elective, so-called "prophylactic" tracheotomy could very well be deferred until there is a clear indication for operation. Actually these cases require expert care and excellent equipment; otherwise, no matter what is done, the results will be poor.

All efforts should be made to get the patient to relax and cooperate; confidence must be instilled in them and any appearance of anxiety and excitement must be avoided. Certainly in a patient who is emotionally unstable and will not cooperate, the wiser thing would be to perform an earlier tracheotomy.

There are times when it may be extremely difficult to tell whether a patient's respiratory difficulty is due to central disturbance of the respiratory center or to pharyngeal secretions. In that case a bronchoscopy could be done for verification or even a tracheotomy would be justified even though it might prove to be ineffective.

Piszczek[29] states that, ". . . . the decision whether or not a patient can be benefited by tracheotomy is a very serious matter. A tracheotomy may be of great value when the patient has a continuous problem with his salivary and bronchial secretions . . . I have observed several almost miraculous recoveries following tracheotomy, while, on the other hand, I have seen a few fatalities immediately following surgery. I feel, however, that if there is a consistent 'drainage' problem of the salivary and bronchial secretions, a tracheotomy should be done."

Wilson[44,45] feels that tracheotomy is a radical step but is often life-saving. All will agree with him when he says, "If the pharynx cannot be kept clear enough so that the patient can get the needed rest, a tracheotomy should be done . . . In a patient with pharyngeal paralysis whose every breath must be

calculated and planned and a continual alert must be maintained in order to expel accidentally aspirated secretion, fatigue gradually develops. This must certainly be prevented."

It is certainly a difficult matter to decide at which point in the course of the disease a tracheotomy should be done, if it is to prove life-saving, because there is usually no single sharply defined indication, except abductor paralysis of the vocal cords, which requires immediate tracheotomy. However, when proper postural drainage and aspiration (both pharyngeal and bronchial) are ineffective in allowing the patient to rest and sleep, a tracheotomy is necessary and one ought not to wait for severe choking attacks with cyanosis to prove its necessity.

Finally the criteria for the performance of a tracheotomy cannot be hard and fast; each case is a law unto itself. The decision will depend upon the physician's experience in the management of these cases. The adequacy of the facilities at his disposal, including the quality of nursing care, must be important factors in this decision.

In general, the laryngologist plays a minor part in the polio team, but in this group of cases he must be prepared to share a large part of the responsibility. Therefore, he should be asked to see these patients early, so that he can observe them in the light of his specialized experience and determine the type and progress of obstructive factors. This would help him determine the most propitious time to intervene, before serious damage can occur from anoxia. In small communities where there is not enough polio to give each man adequate training and experience in the handling of these cases, a polio team should be set up, and the direction of the severe cases transferred to this team. Certainly at least 2 laryngologists should be part of the team, in order that one could be on constant call.

Technique of Tracheotomy. The performance of a routine tracheotomy will not be discussed here. (For a description of the minute details concerning this operation the interested reader is referred to the writer's book, "Acute Laryngotracheobronchitis," published by Grune & Stratton, 1949.) Special considerations required because of the unique conditions that obtain in poliomyelitis, particularly when the respirator has to be used, are outlined below.

If time permits and the patient can understand, it would be wise to explain that he will be unable to talk after the operation, but will again be able to speak at a later date.

1) Tracheotomy may be performed either under local anesthesia or by means of endotracheal anesthesia, whichever is deemed more suitable. In children particularly, a general anesthetic is recommended, some preferring the use of avertin. If necessary, curare may be given to relax the neck muscles and make the head freely movable.

2) Use of the bronchoscope. If there is little or no respiratory obstruction or if a patient's lack of cooperation precludes its use, the bronchoscope may be dispensed with. In all other cases, it is wiser to insert a bronchoscope (or endotracheal tube), both to assure free breathing during the operation and to act as a guide upon which to cut down. This will help prevent the development of pneumothorax and mediastinal emphysema. In the event that there is paralysis of the vocal cords or severe laryngeal spasm, an endotracheal tube is essential, a mask obviously being ineffective.

3) A so-called high tracheotomy, through the second tracheal ring, should be performed, so that if a

respirator is later required the tracheotomy tube will remain on the outside.

4) Be prepared to cope with bleeding from the isthmus of the thyroid gland which may have to be cut.

5) Always use the largest tube that can be inserted comfortably, being careful that there is no excessive pressure, which could cause necrosis of the cartilage. In children, be sure that the tracheotomy tube does not rest on the bifurcation of the trachea. Some have advised cutting off the end of the tube in such a situation; my practice has been to add 2 or more gauze pads placed under the flange of the tracheotomy tube. This will keep the tube from extending too far down the trachea.

6) If the patient is to be placed in a respirator immediately following tracheotomy, respirations can be maintained by the use of a tight-fitting anesthesia mask, with oxygen insufflated by manual pressure of the bag. If a Bennett flow-sensitive positive pressure machine is available, this can be used during the operation. In this way the tracheotomy is done under a closed system of anesthesia, preferably over a bronchoscope.

7) If the patient is already in a respirator and cannot breathe well enough to permit carrying out a tracheotomy with the respirator opened up, the following techniques may be employed:

a) Using a positive pressure mask (Bennet or other type) the patient can be pulled far down into the opened respirator, but with the head still outside. With this technique the neck must be pulled up through the collar after the operation and the respirator closed and turned on as soon as the trachea is opened. A finger should be placed over the tracheotomy tube opening and the positive pressure oxygen continued until all is ready and the respirator is working again.

b) The patient's body, including the head, may be pulled down inside the opened respirator and the anesthetic or oxygen can be applied through the collar opening of the respirator. As soon as the trachea is opened the oxygen tube is attached directly to the tracheotomy tube and the patient's head and neck drawn through the collar opening. This latter method has been deemed more suitable.

Another suggestion for keeping a respirator patient out of the respirator is the use of the Electrophrenic Respirator.

A number of devices to hold the rubber collar away from the tracheotomy tube have been suggested. Some of these follow:

Galloway[15] advises the use of a "gray iron" bar $\frac{3}{8}$ inch by $\frac{3}{4}$ inch bent at a suitable angle and held under the iron flange over the neck outlet to hold the collar away from the tube.

Miller and Buck[24] also use a metal flange to hold the rubber collar down and away from the tracheotomy wound.

Bower *et al.*[6] use a spoon-shaped device which presses the flexible collar away from the tube. Patients do not like the sponge rubber respirator collar. Therefore it is kept away from the neck, but retained in order to support an additional thin koroseal diaphragm snug at the neck. Soft towels are placed around the neck inside of the machine; this seals better and is more comfortable. There is also a diaphragm with a zipper on the market.

Allen and Landmesser[1] describe the emergency use of an abdominal retractor, a roll of 1-inch gauze and a band of 2-inch stockinet, 18 inches long, stuffed with cotton. "The retractor blade is hooked underneath the anterior margin of the rubber respi-

rator collar from within the respirator, and the collar is retracted toward the patient's suprasternal notch. A double length of 1-inch roller gauze is tied to the retractor handle and brought up through the hole provided by removal of the screw plug from the top center surface of the respirator cylinder. When the proper amount of tension has been applied to the roller gauze to provide sufficient retraction of the respirator collar, the screw plug is replaced, and the roller gauze is thereby fastened at the point from which traction proves to be at an optimum angle to prevent leakage from distortion of the collar. The band of cotton-padded 2-inch stockinet is wrapped comfortably around the patient's neck to prevent minor leaks and chafing. A soft gauze pad may be placed under the retractor handle so that it rests comfortably on the patient's chest."

Strobel and Canfield[37] advise the use of a special collar which should be used whenever there is the possibility of a tracheotomy on a respirator patient, because the time spent in changing the usual foam-rubber collar of the respirator to the tracheotomy collar is often greater than the time needed for the tracheotomy.

Peterson and Ward[28] advise the use of a collarless respirator devised by Monaghan when doing a tracheotomy on a respirator patient.

The writer has used a ribbon abdominal retractor placed horizontally between the steel collar and the respirator. It was molded so that it pushed the rubber collar toward the respirator, holding it away from the tracheotomy tube. This was used in an emergency and proved both simple and satisfactory.

Bower and his associates[6] have developed an improved tracheotomy tube in order to overcome some of the objectionable features in the standard tracheotomy tube, as they apply to its use in tracheotomized respirator patients. They also have special adapters for connecting the mobile Bennett positive pressure respirator units to the tracheotomy tube and bronchoscope.

Post-Operative Care. ASPIRATION. Secretions should be removed at intervals of 15 to 30 minutes, as best suited in the particular case. The catheter should have smooth rounded ends and only one or 2 side openings. Nurses must be taught to use extreme caution and gentleness. In order to avoid trauma to the tracheal mucosa the rubber tube should be pinched off during its insertion, which is timed with inspiration. When necessary, the rubber tube should be inserted down to the bronchi in order to remove inspissated plugs. The catheters can be sterilized in a solution of Zephiran, 1:3000.

POSTURAL DRAINAGE. The foot of the bed or respirator should be raised at an angle of 25° to facilitate drainage by gravity. However this should be done only for a period of 5 to 10 minutes out of every hour, because longer periods cause a marked fall in the tidal air, as demonstrated by Bower and his associates[6]. It is a good idea to instill a half dropper-full of a solution of sterile 3% sodium bicarbonate, normal saline solution or penicillin (5000 units per cc.) before raising the foot of the bed, and then aspirating while the head is lowered. The patient should also be encouraged to cough at this time and helped by placing the finger over the tracheotomy opening during expiration. If the patient is unable to cough, he can be helped by applying manual pressure to the thorax.

HUMIDIFICATION. The patient should be in a warm, moisture-laden atmosphere, with the temperature about 70° to 75° F. and the relative humidity 80 to 90%. If the patient is given oxy-

gen, carbon dioxide and moisture should be added.

Feeding. An adult should receive from 2500 to 3000 cc. of fluids, roughly in the proportion of one-third isotonic sodium chloride or Ringer's solution and two-thirds of 5% dextrose in water. It is important to see that the patient does not become dehydrated so that the secretions get too viscid. Overhydration can result in cerebral or pulmonary edema. After the first few days a protein hydrolysate and vitamins (500 mg. B complex and 500 mg. ascorbic acid) may be given intravenously. Gavage feeding can be started after the patient begins to swallow.

Ventilation. A newly devised respiratory ventilation meter (Bennett)[6] has been helpful in determining whether the patient in the respirator is obtaining adequate ventilation. By setting the negative respirator pressure and positive oxygen pressure at various strengths and checking the meter, optimum pressures can be arrived at. The rates and pressures must be checked carefully and regularly several times a day. It has been found that in tracheotomized respirator cases receiving added positive pressure breathing, there is less variation in the pH of the blood and a significant decrease in the frequency of pulmonary acidosis.

Antibiotics. Penicillin should be given routinely in these cases to combat and prevent infection. Terramycin can be given intravenously. Penicillin may also be given as an aerosol.

Roentgenograms of the Chest. These should be taken routinely after the tracheotomy and whenever warranted thereafter.

Removal of Tracheotomy Tube. The tracheotomy tube should not be removed until quite some time after the patient is out of the respirator, because many patients get repeated episodes of atelectasis, due to their inability to cough effectively. It would be wiser to leave the tube in too long rather than too short a time. The tube should first be plugged for 2 days to a week before removing it entirely.

Nursing. These patients present a very difficult nursing problem. Therefore, only highly competent nurses, well trained in the care of tracheotomized patients, should be assigned to these cases. An inexperienced nurse may fail to prevent or correct an episode of cyanosis which may lead to a fatal outcome. It devolves upon the attending physician to instruct each nurse in the care of each individual patient pointing out the problems, the dangers and the treatment in the most detailed manner.

Positive Pressure Oxygen Apparatus. Glaser[18] designed a positive pressure oxygen apparatus primarily to remove accumulated secretions from the pharynx, but no provision was made for humidification of inspired gases or control of inspiratory and expiratory pressures. Kubicek *et al.*[21] discuss the physiology of respiration during poliomyelitis and describe the construction and operation of a tracheotomy inhalator which provides humidification of the inspired air and has simple arrangements for the optional use of positive pressure during expiration and for increasing the positive pressure on inspiration in case of emergency. This inhalator can be made in a few hours almost entirely from stock laboratory supplies and hospital oxygen therapy equipment. It requires a special fitting called a T-1 attachment, by which the tracheotomy tube is attached to the inhalator.

Its use is valuable because after tracheotomy the tracheal secretions are thick and viscid and tend to obstruct the airway. This is an especially important problem when there is super-

imposed paresis of the diaphragm and intercostal muscles. When needed, greater humidification is obtained by nebulizing saline or penicillin solution directly into the tracheotomy tube. The easily visualized excursions of the breathing bag and the intermittent bubbling of the expired air through the manometer facilitate the observation of critical patients by the special nurse. By proper use of the inhalator, the physician can determine the indication for suction of the tracheobronchial tree below the level of the tracheotomy. (A simple way to judge the need for aspiration is to place the tip of the fingers over the tracheotomy opening and note whether there is a strong, free blast. A. H. N.) Such aids are useful during an epidemic. The inhalator is *not* a device for artificial respiration.

The Bennett[6] flow-sensitive intermittent positive pressure breathing unit is a mobile pressure breathing and resuscitation apparatus which has been of great value in the emergency management of polio patients with respiratory paralysis and in those requiring anesthesia. For example, it has been used for quick artificial respiration to transport and maintain the patient before placing him within the respirator, to maintain respiration during tracheotomy, for pressure breathing therapy (especially when using 60% helium, 40% oxygen mixture for 10 minutes out of the hour to overcome atelectasis), to maintain respiration when the mechanical respirator failed mechanically and to help in expanding the lungs of post-respirator patients. This unit differs from other resuscitators in that it is flow-sensitive. Therefore, in addition to providing automatic cycling at any given rate and pressure desired, it also permits the patient to control the cycling rate and rhythm. The control valve is so designed that it automatically adapts itself to the patient's breathing, rather than requiring the patient to adapt his breathing to the valve. Thus, if the patient initiates his own breathing, the flow-sensitive Bennett valve instantly follows the patient's breathing pattern, and the automatic cycling stops. It starts again only if the patient stops breathing or slows down to an inadequate rate. This unit can be attached to the standard type respirator thus providing positive intra-tracheal (or mask) pressure during inspiration, while permitting free expiration into the atmosphere at zero pressure. In addition there is provided a humidifier attachment to this unit to prevent thickening and crusting of secretions.

Summary. A general review of the problem of respiratory obstruction in bulbar poliomyelitis together with the pros and contras of early tracheotomy in these cases has been presented. An attempt was made to find middle ground which could serve as a basis for treating these desperately ill patients. Special points in the performance of tracheotomy and the after-care as related to the unique conditions that obtain in bulbar poliomyelitis have been outlined.

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BOOK REVIEWS AND NOTICES

DIAGNOSTIC AND EXPERIMENTAL METHODS IN TUBERCULOSIS. By HENRY STUART WILLIS, M.D., Supt. and Med. Dir., North Carolina Sanatoria, McCain, N. C., and MARTIN MARC CUMMINGS, M.D., Dir., Tuberculosis Res. Lab., Lawson V. A. Hosp., Chamblee, Ga. 2nd ed. Pp. 394; 43 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $10.00.

THIS book should have an enthusiastic reception by students, general practitioners, pulmonary disease specialists and laboratory workers alike, for nowhere else is there such a clear and practical presentation of the fundamental laboratory aspects of tuberculosis. The authors of this thoroughly revised edition have achieved a happy blend of important background information and concise step-by-step explanation of various laboratory procedures for both diagnostic and experimental purposes. While touching on many issues which await final decision, such as BCG vaccination, the proper use of tuberculin and the relation of allergy to immunity, a moderate position has been taken which neither slights the conflicting points of view nor adds to controversiality. The bibliography, in itself, constitutes an invaluable source of references in the evolution of laboratory procedures in tuberculosis. All in all, the book can be heartily recommended either for the library shelf or to be kept open on the laboratory table. D. O.

ORAL MEDICINE. DIAGNOSIS AND TREATMENT. By LESTER W. BURKET, D.D.S., M.D., Prof. Oral Medicine and Dean, Univ. of Pa. School of Dentistry. 2nd ed. Pp. 575; 372 ills., including 40 in color. Philadelphia: J. B. Lippincott Co., 1952. Price, $14.00.

DENTISTRY is basically a part of Medicine. By reason of its highly specialized nature and particularly its specific technical aspects, it became completely separated from the parental stem, in some respects to the detriment of both. It is significant that at the University of Pennsylvania there has been long recognized the need for a closer relationship between these two fields. In part, this was achieved by correlated teaching in the basic sciences and more recently in correlated teaching in the clinical years. Then a textbook appeared: Internal Medicine in Dental Practice, by Comroe, Collins and Crane, all physicians, which gave a medical view of the subject and has reached its 3rd edition. The present volume is the 2nd edition of a work produced by an author who is both a physician and a dentist and is primarily a teacher of dentists. Written primarily for dentists, the book should have a great appeal for physicians as well. The numerous illustrations are excellent. Most of the chapters are documented with an extensive bibliography. R. K.

LIVING IN BALANCE. By FRANK S. CAPRIO, M.D., Pp. 246. Washington, D.C.: The Arundel Press, Inc., 1952. Price, $3.75.

THIS book is intended to give directions for understanding one's self and other people. It deals with neuroses, inferiority complexes, undesirable personality traits, unhappy marriage, jealousy, neurotic husbands and wives, alcoholism, suicide, as well as many other topics.

The author, with a well-meaning attempt to give a rule or thumb solution for the many complexities of human maladjustment, has resorted to considerable boldness in interpretation and some dogmatism in many of his statements. Such matters as dream interpretation and happiness are treated with condensed chapters called "Charts." There is no index and there are no references.

O. E.

ARZT-KASSE-VOLKSGESUNDHEIT. By DR. MED. GUSTAV SONDERMANN. Pp. 69. Munich: J. F. Lehmanns Verlag, 1952. Price, DM 4.50.

A German version of the plight of the physician under the yoke of a socialized medical program: a tragic recital that the physicians of this country might read with profit. The reviewer quotes this sentence, of typical Teutonic complexity, that carries a major lesson: "We Germans, in the consuming fires of the last decade, had the opportunity to learn much that is still hidden from other peoples; it remains to be seen whether, in the aggregate, we shall make good use of this opportunity—we physicians certainly want to; and the first thing, that has become clear to us in these times and out of the events of the past, is this: the nature and value of

man, of the individual man, must stand at the center of our thinking and action: every political and economic system which denies to the individual such value and existence also has no place for the physician as we conceive him." R. K.

ALLERGY IN RELATION TO PEDIATRICS. By BRET RATNER, M.D., Prof. Clin. Pediat. and Assoc. Prof. Immunol., New York Medical College. Pp. 228; 12 ills. St. Paul: Bruce Publishing Co., 1951. Price, $3.75.

THERE are presented 16 articles by 17 contributors on various aspects of allergy as observed in children. The material is the substance of a Panel Discussion held at the Annual Meeting of the American College of Allergists in 1949. It offers a wealth of practical information in this important field. R. K.

SOMATIC AND PSYCHIATRIC TREATMENT OF ASTHMA. Edited by HAROLD A. ABRAMSON, M.D., Assoc. Phys. and Chief, Allergy Clinic, Mt. Sinai Hosp., New York. Pp. 751; 90 ills. Baltimore: Williams & Wilkins Co., 1951. Price, $11.00.

THIS book is a compilation of 35 chapters, by 34 contributors, on various aspects of allergy, clinical, theoretical and problematic. They are arranged in sections entitled, "Basic Concepts, General Testing and Treatment; Nature of Inhalant Allergens and their Therapy (sic); Somatic Therapy; Psychotherapy; and Special Geography." There is unnecessary duplication and not too good a correlation. There is undue emphasis on much that is controversial. There is heavy emphasis on the psychotherapeutic approach with such concepts as "parentectomy." The book is not recommended. R. K.

STANDARD VALUES IN BLOOD. Edited by EBRETT C. ALBRITTON, A.B., M.D. Pp. 199. Dayton, Ohio: Wright-Patterson Air Force Base, 1951.

THIS work constitutes the first portion of a Handbook of Biological Data which has been undertaken by a special committee of the American Institute of Biological Sciences, operating under the National Research Council. Standard values in blood for man and other vertebrates are given in tabular form, with sections devoted to the following: Physical Properties; Coagulation Phenomena; Blood Groups; Erythrocytes and Hemoglobin; Leukocytes; Blood and Bone Marrow Cells; Water, Carbohydrates, Lipids, and Proteins; Amino Acids and Non-Protein Nitrogen Compounds; Phosphorus and Sulfur Compounds; Vitamins, Hormones and Enzymes; Electrolytes, Minerals, Gases, and Acid-Base Values; Effects of Radiation and Storage; and Effective Blood Levels of Therapeutic Agents. Some idea of the completeness and reliability of the report can be judged from the fact that the data have been supplied and authenticated by over 600 leading investigators in biology and clinical medicine.

This volume will be welcomed by clinicians, clinical pathologists, and research workers in many fields. C. Z.

BLOOD CLOTTING AND ALLIED PROBLEMS. Transactions of the Fourth Conference, January 22-23, 1951, New York, N. Y. Edited by JOSEPH E. FLYNN, Dept. of Path., College of Physicians and Surgeons, Columbia University. Pp. 271; 81 ills. New York: Josiah Macy, Jr., Foundation, 1951. Price, $4.00.

THIS is a verbatim report of the Fourth Conference on Blood Clotting and Allied Problems which met January 22-23, 1951. As in preceding transactions, the discussions are informal and represent the views of a number of outstanding authorities on the following topics: Methods for Direct Investigation of Factors Leading to Thrombosis; Studies on Canine Hemophilia; Characteristics of Blood Platelets; Their Significance in Thrombus Formation; Morphological and Physiological Studies of Platelets and Hemostasis; Antithrombin—Alpha Tocopherol; and the Transition of Fibrinogen to Fibrin. In addition, there is a section on "Polarographic Studies of the Fibrinogen-Fibrin Reaction."

While the volume is perhaps of greatest value to workers investigating the complexities of blood coagulation, it also contains many worthwhile practical suggestions for application in medicine and surgery. C. Z.

PHARMACOPOEIA INTERNATIONALIS. Pp. 406. Geneva, Switzerland: World Health Organization, 1951.

THIS book is a milestone in human progress. Efforts to produce an international pharmacopoeia began in 1874 and have continued at intervals ever since. They have culminated in the issuance of this volume. It is not intended to be a legal pharmacopoeia

binding on any country but it could be so adopted by the pharmacopoeial authority of that country. Form and arrangement follow current practice with most international pharmacopoeias. An international nomenclature of drugs uses the Latin language for universality. In addition to the descriptions of drugs, there are 43 appendices that give such things as lists of reagents and test solutions, tests for heavy metals, various tests for potency, assay and purity and lists of usual and maximal doses of drugs. Volume 2 will deal with data on injections, sterility tests, pyrogen tests and others. R. K.

UROLOGICAL PATHOLOGY. By PETER A. HERBUT, M.D., Prof. of Pathology, Jefferson Medical College of Philadelphia. Two volumes. Pp. 1221; 527 ills. Philadelphia: Lea and Febiger, 1952. Price, $24.00.

DR. HERBUT has written a complete text on the pathology of the urinary system and the male genital system and has included a section on the adrenal gland for good measure. This opus appears to be directed principally toward the urologist as a collection of everything he should know about his specialty. A rigid pattern of discussion is used. The matter is presented according to regions and a summary of the normal anatomy and physiology precedes the account of the diseases related to each region. Each important condition which may involve this region is then presented under the headings of definition, distribution, cause, clinical manifestations, gross appearance, microscopic appearance, complications, clinicopathological correlation, diagnosis, treatment and prognosis.

As one reads consecutively through these volumes one gets the impression that there is considerable overlapping. A good deal of print might have been saved if the disease processes had been discussed as a whole and the regional variations dealt with in a summary.

This method of presentation may be defended on the basis of the use for which the book is intended. The urologist is inclined to consider a disease in terms of the altered physiology of the region involved. A papilloma of the bladder may be quite different in its manifestation than one in the ureter for example. Thus the urologist is probably less interested in a concise presentation than he is in a thorough discussion which he can find without reading through a considerable material in which, at the moment at least, he is not particularly interested. If the book is meant for the clinician who is treating disease of the urogenital tract I believe it achieves its purpose. If it is also intended as a text for medical students as the publishers claim I am afraid we shall have to designate more time for this subject than the usual curriculum allows.

Certain clinicians may comment upon the advisability of including a discussion of treatment in a text of pathology. In defense of the presentation it should be said that this aspect is very brief and is probably permissible in order to complete the disease picture.

If for no other reason, these volumes should be of great value for their bibliographies. At the end of each regional section there is a list of references most of which run into the hundreds. It is apparent that Dr. Herbut has carefully sifted the literature of the last twenty-five years and has put down a consensus of nearly everyone who has written in this field.

Again it seems to this reviewer that this work is an important one for the urologist and those who are training in this specialty. Dr. Herbut has used his teaching talents in organizing and coordinating the knowledge in this particular field and in presenting it in a readable manner. E. A.

THE ENZYMES. CHEMISTRY AND MECHANISM OF ACTION. Edited by JAMES B. SUMNER, Cornell Univ., and KARL MYRBÄCK, Biokemiska Inst., Stockholm. Vol. 2, Pt. 2. Pp. 791-1440; ills. New York: Academic Press, 1952. Price, $14.00.

THIS volume concludes the encyclopedic work on the chemistry and mechanism of action of the enzymes, published in 4 parts, a total of 2801 pages. For a general discussion and review of the first 3 parts, reference should be made to the Am. J. Med. Sci., **221**, 474, **222**, 609, 1951, and **223**, 346, 1952. The present volume contains 14 chapters written by 16 specialists in various fields of enzymology. The subjects covered are: Bacterial Fermentation by S. R. Elsden; Enzymes in Detoxication by Frederick Bernheim; Urea Synthesis by H. A. Krebs; Peptide Bond Synthesis, and Enzymatic Synthesis of Glutamine by Philip P. Cohen; Synthesis of Acetylcholine (Choline Acetylase) by Klas-Bertil; Oxidative Assimilation by Microorganisms by C. E. Clifton; Enzymatic Mechanisms of Carbon Dioxide Fixation by Severo Ochoa; Carbohydrate-Fat Conver-

sion by F. L. Breusch; Photosynthesis in Green Plants by Walter E. Loomis; Bacterial Photosynthesies by C. B. Van Niel; Nitrogen Assimilation by Artturi I. and Niilo Rautanen; Tumor Enzymology by Jesse P. Greenstein and Alton Meister; Enzyme Technology by A. F. Langlykke, C. V. Smythe, and D. Perlman.

Like the preceding volumes, the final part is an indispensable tool for workers in almost any field of the chemical and biological sciences. B. L.

DIABETES AND PREGNANCY. By RALPH A. REIS, M.D., EDWIN J. DECOSTA, M.D., and M. DAVID ALLWEISS, M.D. Pp. 78; 4 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $2.50.

THE authors of this short monograph are well known in obstetrical circles for their recent report of a series of personally managed diabetic pregnancies in which excellent results for mother and infant were obtained without the use of adjunctive sex steroid therapy. Their exposition, based upon their clinical studies and a brief survey of recent literature, is a concise review of the practical aspect of the subject. In their appraisal of various methods of therapy, they modestly acknowledged that their own good results have been due in part to their encountering a high proportion of the milder forms of diabetes among their patients. This objectivity, and the very apparent care and skill with which they have managed their patients, enhances the value of their views, and makes their booklet one of the most readable and useful accounts of diabetic pregnancy that has appeared in recent years. C. B.

CASE HISTORIES IN PSYCHOSOMATIC MEDICINE. By THE STAFF OF THE PSYCHIATRIC SERVICE, MASSACHUSETTS GENERAL HOSPITAL BOSTON, MASS. Edited by HENRY H W. MILES, M.D., STANLEY COBB, M.D., and HARLEY C. SHANDS, M.D. Pp. 301; 4 ills. New York: W. W. Norton & Co., Inc., 1952. Price, $4.50.

THIS is a compilation of psychosomatic conferences previously published in various medical journals. They serve the same purpose in this era of the integration of psychiatry and medicine that clinico-pathologic conferences served in relation to the study of organic disease. For example, the principles learned in psychiatry are applied to the doctor-patient relationship as it exists in medicine and surgery and this is illustrated by short but appropriate case reports. The psychological traumatic effects of tonsillectomy—ordinarily regarded as an innocuous operation—are pointed out in several conferences. Important material is discussed regarding the dangers of deep psychotherapy in ulcerative colitis and here, too, one notes the opportunity for cooperation between medicine and surgery and psychiatry. There is a good discussion of anorexia nervosa; some rare neurological cases; as well as many of the commoner problems that present themselves in general hospital work.

The material is not dealt with exhaustively from a psychological standpoint and hence will not have great value for the dynamically trained psychiatrist, but they are written for a general medical audience and for that purpose are recommended. E. W.

TRANSACTIONS OF THE AMERICAN GOITER ASSOCIATION. Pp. 506; illustrated. Springfield, Ill.: Charles C Thomas, 1952. Price, $12.50.

THIS volume includes the papers which were presented at the 1951 Annual Session of the American Goiter Association. It is a particularly valuable book and should be in the library of everyone interested in thyroid disease. There are fascinating articles on both clinical and experimental subjects.

W. P.

THE FIGHT AGAINST TUBERCULOSIS. AN AUTOBIOGRAPHY. By FRANCIS MARION POTTENGER, M.D., Medical Director, Pottenger Sanatorium, Monrovia, Calif. Pp. 259; 4 ills. New York: Henry Schuman, Inc., 1952. Price, $4.00.

THE author was born in 1869 on an Ohio farm. When 10 years old his interest in science and especially medicine was inspired by the family physician who attended him for a severe fracture—dislocation of the right elbow. College, medical school (a two year course), a postgraduate year in Europe, and young Pottenger was ready to embark upon general practice. When his wife developed tuberculosis, Pottenger learned how little was known about the treatment of that prevalent and usually fatal disease. By personal contact and correspondence with students of tuberculosis he made himself a specialist, and eventually became recognized as one of the outstanding American phthisiologists.

In his autobiography Dr. Pottenger reviews his long, busy career. The establishment of the Pottenger Sanatorium at Monrovia, California, his contacts with other pioneers, both here and abroad, teaching, research, founding societies, public health work—these and other activities made for a very full life.

The book is written in clear though never pretentious, technical or stylistic language. It should be of interest to medical and lay workers in the field of tuberculosis. R. C.

ELEMENTARY MEDICAL STATISTICS. By DONALD MAINLAND, D.Sc., Professor of Statistics, New York University College of Medicine. Pp. 327; 23 figs., 2 charts. Philadelphia: W. B. Saunders Co., 1952. Price, $5.00.

THIS text is developed to provide statistical tools for medical researchers, to be used to test past reports and to scrutinize current investigation. The author has limited himself to a few easily applicable methods, which are illustrated by practical examples. There is an introductory section, prepared as the text for 16 one-hour lectures to premedical or first year students, and an advanced section for researchers proper. Few medical schools can afford this many lectures, and it is even doubtful that elementary medical students will ever need this much statistical training to practice the art of healing. Courses of instruction for beginning medical artisans and graduate medical researchers cannot be compatible. The text includes many practical examples, in fact, it bristles with numbers. The author has, perhaps, overemphasized the practical aspect at great cost in understanding the continuity of the statistical philosophy that must also be included. Therefore the text is very difficult for first year students, unless extraordinary preceptors are also available. R. P.

HISTOPATHOLOGICAL TECHNIC. By ARAM A. KRAZIAN, Sc.D. and R. B. H. GRADWOHL, M.D. 2nd ed. Pp. 349, 131 ills., and 7 color plates. St. Louis: C. V. Mosby Co., 1952. Price, $6.75.

KRAZIAN's original "Histological Technic" has been expanded to approximately twice its size in this new edition. This expansion has not necessarily improved its usefulness in all respects. The older book was a collection of routine methods of tissue sectioning and staining arranged in the simplest manner, a manual in every sense of the term. It served admirably as a text for students of medical technology because it was brief and practical. Dr. Gradwohl's larger and more complete volume serves as the standard laboratory guide and reference book. Thus the new volume, in which Dr. Gradwohl has collaborated, is made more complex (and expensive) for the student yet contributes nothing that the larger book has not had for many years.

This volume will find its principal use in the hospital laboratory of pathologic anatomy. Actually, it fills a long felt need here by taking the place of Mallory's manual which has been out of print for several years. For this purpose it should enjoy a wide usage.

E. A.

NEW BOOKS

Final Report of International Conference on Science Abstracting, convened by the United Nations Educational, Scientific and Cultural Organization, in Paris, from 20 to 25 June, 1949. Pp. 192; 10 ills. New York: Columbia University Press, 1952. Price, $2.00.

Report on the Activities and the Meeting of the Co-ordinating Committee on Abstracting and Indexing in the Medical and Biological Sciences. Pp. 92. United Nations Educational, Scientific and Cultural Organization (American agents, Columbia University Press, New York), 1952. Price, $.85.

Atlas of Framboesia. By K. R. HILL, R. KODIJAT AND M. SARDADI. Pp. 19; 42 ills. Geneva: World Health Organization, 1951. Price, $1.00.

THE purpose of this publication is to describe with the aid of photographs the skin manifestations of yaws, and to present a nomenclature for these lesions. The pictures are well done and the accompanying text lists all current synonyms. The clinical description should be of particular use to doctors and nurses in the field.

Memorie e Comunicazioni Scientifiche 1931-*1951.* By PROF. CESARE SERONO. Pp. 509, illustrated. Rome: Instituto Nazionale Medico Farmacologico Serono, 1952.

THERE are presented reprints of 41 articles and addresses in the field of biology and opotherapy which the author published between 1931 and 1951.